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THE EFFECTS PRODUCED BY VARIOUS TYPES OF PUMP-OXYGENATORS DURING TWO-HOUR PARTIAL INFUSIONS IN DOGS

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A 30-MINUTE PERIOD of total cardiac by-pass, with a cross-chest incision and a right ventriculotomy, has become a fairly well accepted test procedure in the laboratory. It is quite a traumatic procedure, and results depend upon many important variables, such as the condition of the dog, the skill of the operator, the amount of anesthetic agent required, and the supportive care given postoperatively. The wide variation in survival rates has often been attributed to the type of apparatus used. The factors mentioned above may have been of much greater importance.

In order to evaluate the effects caused by pump-oxygenators, we thought that more clear-cut results might be obtained by using a partial perfusion technique which causes few complications and a low morbidity and mortality rate in control animals. Adverse effects in the experimental animals might then be more reasonably attributed to the pump-oxygenator employed, than to other variables.

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METHODS

Mongrel dogs, weighing from 10 to 21 Kg., were anesthetized with sodium pentobarbital (30 mg./Kg.) and the trachea was intubated. Plastic cannulae were inserted into the superior and inferior venae cavae through femoral and jugular veins for the collection of venous blood. Arterialized blood was pumped back from the oxygenator through either carotid artery (which was divided) via a plastic cannula inserted 3 cm. proximally, care being taken to avoid passage of the catheter tip into the bracheocephalic trunk (Fig. 1). In some experiments, the arterialized blood was returned through a femoral artery rather than a carotid artery. One femoral artery was cannulated for recording arterial pressures during all experiments.

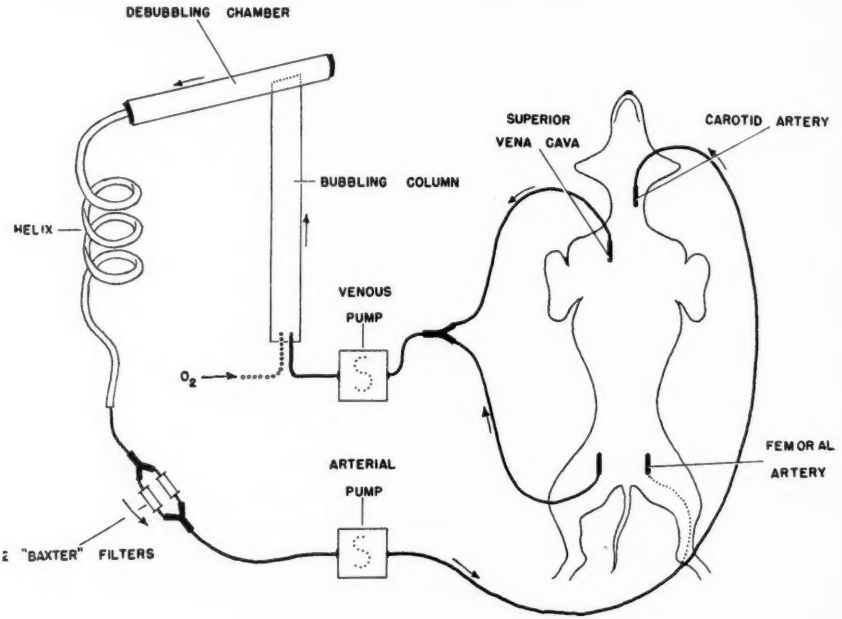


Fig. 1.—This is a diagram of the extracorporeal circuit used. (Dotted line indicates femoral artery perfusion used in Group 3.)

Heparin (2 mg./Kg.) was injected intravenously and the perfusion was carried out at a flow rate of 40 c.c. per kilogram per minute for 2 hours. It should be noted that this was a partial perfusion, and that the venous return not passing through the extracorporeal circuit continued to pass through the heart and lungs in the usual manner. Arterial pressure and heart rate varied only slightly from pre-perfusion levels during the 2-hour period. One hundred per cent oxygen was used in the oxygenator and the dogs developed shallow respirations or became apneic soon after the beginning of the perfusion.

A mechanical respirator was then used until the animal could breathe adequately again without assistance. The rectal temperature usually had drifted down to 32° to 34° C. at the end of the 2-hour perfusion.

Postoperatively, the dogs were observed for periods up to 10 days and then sacrificed. The significant complications which occurred were related to the central nervous system and were manifested by abnormalities of gait, state of consciousness, and responses to environmental stimuli.[1] The degree of neurologic deficit was classified on clinical examination as mild, moderate, or severe. Dogs with mild brain damage walked on the first post-perfusion day, but with an abnormal gait, and responses to stimuli were sluggish, although usually appropriate. Those with moderate brain damage could not stand or walk on the first post-perfusion day and responded very sluggishly to external stimuli. Some seemed to be deaf and blind. Dogs with severe brain damage were comatose or remained almost motionless, with occasional uncoordinate movements of the extremities.

There was a tendency toward improvement, and some animals had no residual clinical abnormality after 5 to 10 days.

At the time of autopsy, the brains of dogs with clinical evidence of neurological abnormalities and the brains of representative animals in other groups were examined grossly and microscopically.

Several methods of perfusion were used. A description of each experiment and the number of dogs in each group is shown in Table I.

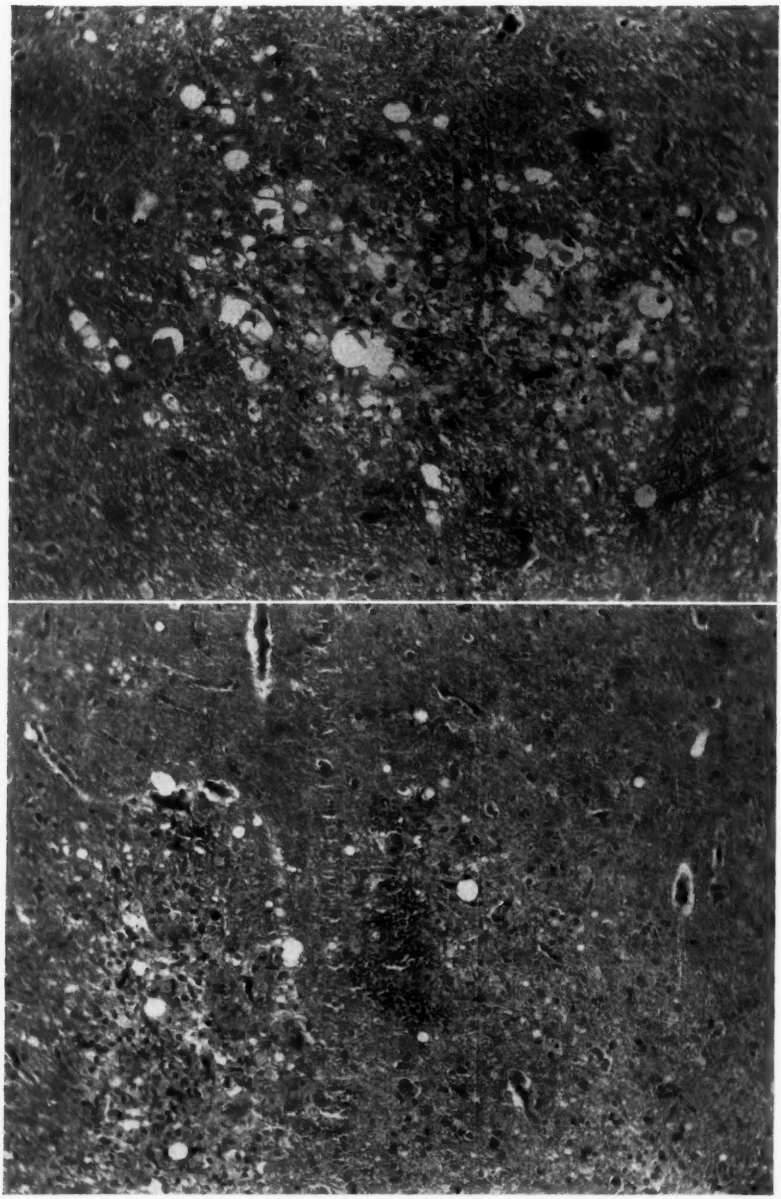
TABLE I. SUMMARY OF EXPERIMENTS

GROUP	EXPERIMENT	NUMBER OF DOGS	NEUROLOGIC ABNORMALITIES			
			NONE	MILD	MODERATE	SEVERE
1	Bubble oxygenator 4:1, O_2:blood ratio Arterial catheter in carotid artery	4	1	2		1
2	Same as No. 1 except 8:1, O_2:blood ratio	8		1	2	5
3	Same as No. 2 except arterial catheter in femoral artery	3	3			
4	Same as Nos. 1 and 2 except no O_2 bubbling Arterial blood from femoral artery	3	3			
5	Film oxygenator, screen type Arterial catheter in carotid artery	4	4			
6	Film oxygenator, rotating disc type Arterial catheter in carotid artery	3	3			
7	Same as No. 4 except excess antifoam	2				2
8	Same as No. 2, except for funnel-shaped reservoir beyond filter	5	5			

RESULTS

In Groups 1 and 2, using the DeWall bubble-oxygenator,[2] with an oxygen to blood flow ratio of 4 to 1 in 4 dogs, and 8 to 1 in 8 dogs, neurologic abnormalities were present in all except one of the 4 to 1 group. A higher rate of oxygen flow appeared to cause more severe brain damage. On gross examination of the brains of 3 animals, small areas of focal necrosis were seen in 2. Lesions characteristically associated with embolism and infarction were

A.



B.

Fig. 2.—*A* and *B*, These are microphotographs from the brain of a dog in Group 2. A typical area of infarction is shown in each.

seen microscopically in all 3 (Fig. 2). In these experiments, some of the blood from the extracorporeal circuit undoubtedly passed up the intact carotid artery and the vertebral arteries to the brain.

In Group 3, we tried to find out if the brain damage was caused by blood which passed through the pump-oxygenator. Under these circumstances blood would probably not reach the brain before passing through a capillary bed because cardiac output was adequate to prevent significant retrograde injection up the aorta. The 3 dogs in this group had no brain damage in spite of the fact that they were perfused at an oxygen-blood ratio of 8 to 1.

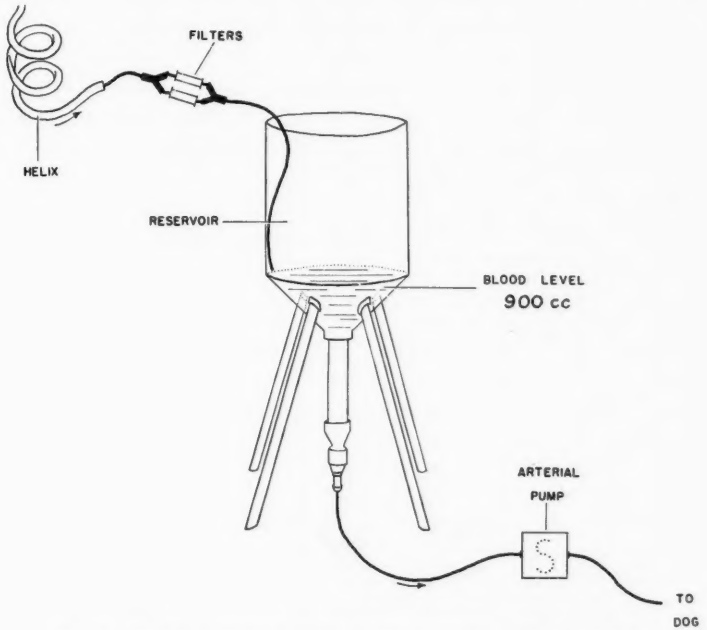


Fig. 3.—This is a diagram of the Lucite reservoir used in Group 8.

In Group 4, blood was withdrawn from the femoral artery and passed through all elements of the DeWall oxygenator except the bubbling column. No oxygen bubbles were used. It was returned to the aorta as in Groups 1 and 2 through the carotid artery. None of these dogs had evidence of brain damage. This indicated that the damage seen in Groups 1 and 2 was associated with bubbling oxygen through the blood.

In Group 5, a screen type film oxygenator[3] was used. Return of the blood oxygenated by this method through the carotid artery caused no evidence of brain damage in 4 animals.

In Group 6, there was no evidence of neurologic deficit when a film oxygenator of the rotating disc[4] type was used in 3 animals.

In Group 7, the possibility that Dow Corning Antifoam-A used in the bubble-oxygenator might cause embolization was investigated, since droplets of antifoam had been detected from time to time in the arterial lines beyond the filters in other experiments. This included perfusions in which an attempt was made to keep the amount of antifoam to the absolute minimum. Arterial blood was passed from the femoral artery through the bubble oxygenator without bubbling as in Group 4, but a larger than usual amount of Antifoam-A was applied to the walls of the debubbling chamber. Both dogs had severe brain damage, presumably due to embolization by droplets of antifoam. The amount of antifoam placed in the debubbling chamber was estimated to be three or four times that usually employed, although the relative quantities cannot be stated with certainty.

In Group 8, an open Lucite reservoir with a surface area of 300 sq. cm. and a blood volume of 900 c.c. was interposed between the filters and arterial pump of the bubble oxygenator, since it seemed that this might provide an opportunity for the harmful embolic elements to float on this surface rather than be pumped into the dog's aortic arch (Fig. 3). Five dogs were perfused with this reservoir in the system and there was no clinical evidence of brain damage even though the oxygen-blood flow ratio was 8 to 1.

COMMENT

The embolic type of brain damage which was caused by the bubble oxygenator as used in these experiments may have been due to air, fibrin, or antifoam emboli, or to a combination of two or more. We were not able to determine which elements were predominant. Mineral oil was layered over the blood in the reservoir in an attempt to demonstrate oxygen bubbles at the oil-blood interface. We could not see any bubbles, nor was blood from this area seen to contain bubbles when examined microscopically. Many tiny antifoam particles were seen at the blood-oil interface. We could not show that fibrin was being trapped on the reservoir surface, or that the beneficial effect of the reservoir was due to its depulsating action on the blood in the filter and helix.

The absence of brain damage with two different types of film oxygenators suggests that there may be a considerably wider margin of safety with the film method of oxygenation. With the bubble oxygenator, the use of an open reservoir with a large surface area proximal to the arterial pump is an important safety device.

CONCLUSIONS

1. An embolic type of brain damage resulted when a bubble oxygenator was employed in the manner described during 2-hour partial perfusions in dogs. It could not be determined whether these were air, fibrin, or antifoam emboli.

2. There was no evidence of embolization when two types of film oxygenators were used.

3. A device that decreased the embolization of the brain associated with the bubble oxygenator experiments has been described.

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(For Discussion, see page 587)

PHYSIOLOGIC STUDIES UPON PROLONGED CARDIOPULMONARY BY-PASS WITH THE PUMP-OXYGENATOR WITH PARTICULAR REFERENCE TO (1) ACID-BASE BALANCE, (2) SIPHON CAVAL DRAINAGE

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TOTAL cardiopulmonary by-pass for reparative intracardiac surgery has become a conventional clinical procedure at the Heart Hospital. To date, 300 patients have had such perfusions carried out and, with the experience engendered by this daily usage, two broad consequences have become evident. First, because of the benefits to them of visual corrective surgery, patients of all ages and with cardiac disabilities of all degrees of severity are undergoing these perfusion procedures. Second, the duration of these total by-pass procedures has steadily increased with increasing experience so that the average duration of this interval now approximates one hour. Our goal has been to maintain these patients in the safest possible state during this period of extracorporeal circulation. This safety can be achieved best by an accurate appraisal of the physiologic alterations occurring, an estimate of their relative significance and importance, and methods for their control when necessary. Thus, these clinical trends have pointed the way for the experiments reported here.

METHODS

The extracorporeal circuit consisted of an arterial and a venous pump of the multiple finger cam-operated type[1] and a bubble oxygenator of the helix principle[2-6] or a plastic sheet modification of this.[7] One hundred per cent oxygen was used to arterialize the blood and carbon dioxide was allowed to escape freely from it during its passage through the oxygenator.

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Adult mongrel dogs ranging in weight from 5.5 to 25 Kg. body weight and of both sexes were used. After premedication with morphine sulphate (gr. ¼) and atropine (gr. 1/100), they were anesthetized with intravenous sodium thiopental (Pentothal). The level of anesthesia was kept as constant as possible at a light plane by the frequent intermittent administration of further small doses of Pentothal as needed, but in no instance was Pentothal given during the course of the perfusion and only rarely was it necessary to give more after the conclusion of the period of by-pass. Ventilation with air was maintained throughout the experiment* by a cuffed endotracheal tube connected to an intermittent positive pressure cam-operated mechanical respirator. The body temperature of the animals was kept constant at 39° C. by the use of an electric blanket and by maintaining the temperature of the blood in the extracorporeal circuit at this level by immersion of the helix reservoir in a thermostatically controlled water bath or other suitable electric warming device.[7]

A standard right thoracotomy was performed, the azygos vein ligated and occluding tapes placed in position around the cavae cardiac to the azygos and hepatic veins. An arterial cannula was inserted into the right carotid artery isolated in the neck. Venous drainage was effected either by a single long catheter introduced through the external jugular vein and draining both venae cavae, or by two catheters introduced separately into each cava through the right atrial appendage. In some instances, detailed below, a coronary sinus catheter was introduced through a small stab incision in the wall of the right atrium and held in place just within the coronary sinus opening by an encircling silk ligature.[8]

In addition, in a number of dogs, central arterial and venous pressures were recorded in the descending aorta and inferior vena cava, respectively, through fine catheters introduced through the femoral artery and vein. Immediately prior to these cannulations, the animals were heparinized by the administration of 1.5 mg. heparin per kilogram of body weight. As soon as the cannulae had been removed at the end of the by-pass period, protamine sulphate was given intravenously slowly in intermittent doses over a 5-minute period to a total amount of 3 mg. per kilogram of body weight.

The studies were divided into three sections as follows: The first section (Group A) consisted of a group of 5 dogs, constituting the control series. These animals were not perfused, but were subjected to a right thoracotomy and ventilated by the mechanical respirator. Biochemical determinations were made at the beginning and end of a one-hour period with the chest open (Sham Perfusions). The second series (Group B) consisted of 48 dogs subjected to total cardiorespiratory by-pass for a period of one hour at different perfusion rates. In this series, the predetermined perfusion rate was kept constant for each dog throughout this hour. Blood samples for gas analyses and lactic acid determinations were drawn at the beginning and end of the

*Both experimentally and clinically the lungs have been partially and gently inflated during the total by-pass period to lessen complications due to atelectasis.

perfusion period.[1-4] In the third series (Group C) consisting of 9 dogs, oxygen consumption in relation to perfusion rate was determined by subjecting each dog to total cardiorespiratory by-pass at various perfusion rates. Each perfusion rate studied was maintained for at least 15 minutes and the vascular system of the dog thus allowed to stabilize before blood samples were drawn for the determination of arteriovenous oxygen differences. In this group the superior and inferior caval catheters and, in some cases, a coronary sinus

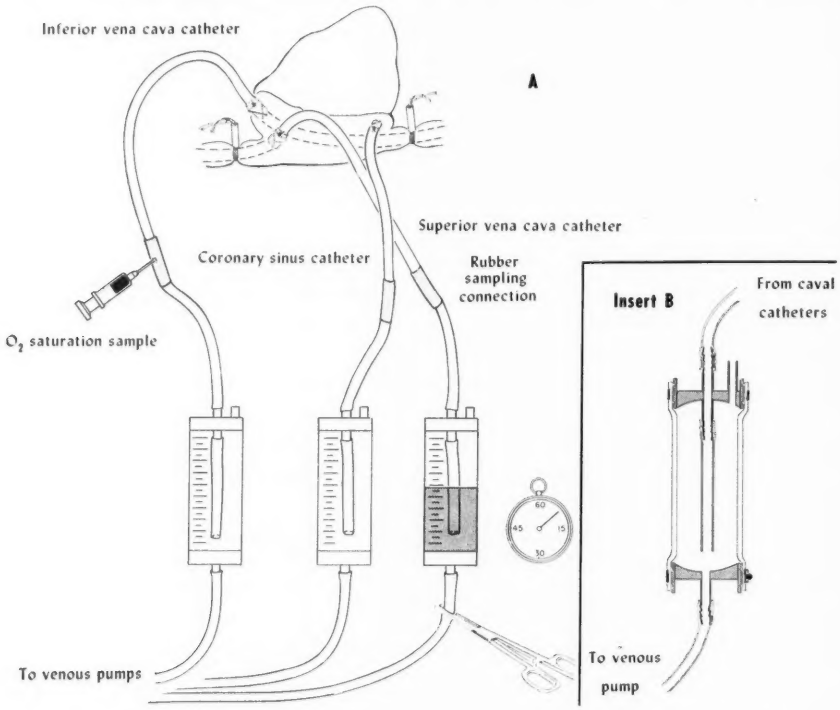

Fig. 1.—Siphon Venous Drainage System. *A*, Experimental system for investigation of different venous drainage areas of the body. Insert *B* shows the venous well used clinically for the perfusions.

catheter as well were drained by gravity siphonage into separate, open graduated chambers. The venous blood from each of these chambers was returned then to the oxygenator by separate venous pumps (Fig. 1). By occluding, temporarily, the outflow from each of these chambers, the exact venous return from each vena cava and the coronary sinus was determined. It is noteworthy that accurate balance between total venous return and the output of the arterial pump was found to exist over the whole range of perfusion rates explored. This relationship was found to be so constant in laboratory studies in over 50 dogs that the measurement of the total venous return from the animal when collected by a gravity venous siphon system was a valid measure

of the arterial perfusion rate. In other words, the flow out of the venae cavae, when collected by gravity siphon drainage, was equal to the arterial inflow over a wide range of perfusion rates.

The plasma bicarbonate concentrations, measured at the different pH's existing, were all converted to a standard point of reference of pH 7.4 for accurate comparison by applying the Peters and van Slyke formula.[9]

RESULTS

In the control group (A), in spite of a marked respiratory alkalosis due to hyperventilation by the mechanical respirator, the average bicarbonate deficit at pH 7.4 was 4.92 mM per liter after one hour under anesthesia and with the chest open. The spread in these observations was from 3.04 to 7.61 mM per liter. The degree of respiratory alkalosis can be judged from the average final carbon dioxide tensions in the arterial blood which was 19.8 mm. Hg with a spread from 17.5 to 29.5 mm. Hg. (Normal values, 35 to 45 mm. Hg.)

In 48 animals (Group B), acid-base determinations (bicarbonate deficit) were made. This deficit varied from 16 mM per liter at a flow rate of 0.22 L. per square meter per minute to 3 mM per liter at a flow rate of 2.6 L. per square meter per minute. It is noteworthy that, above a flow rate of 1.2 L. per square meter per minute, the bicarbonate deficit decreased more gradually as the flow rate was increased.

In 15 dogs of Group B, serial acid-base determinations were made at flow rates varying from 0.4 to 2 L. per square meter per minute, the flow rate being kept constant for each dog for one hour. The results showed that there was a linear relationship between the duration of the perfusion and the development of metabolic acidosis (increase in bicarbonate deficit). These studies also showed that for any particular perfusion rate within this range the oxygen consumption did not change over the duration of this 60-minute perfusion.

Lactic acid determinations were also made in most animals in Group B as a measure of fixed acids. From Table I it can be seen that there is a significant progressive decrease in the excess lactic acid produced as the perfusion rate is increased. The bicarbonate deficit shows a similar decrease with increasing perfusion rates and this is graphically shown in Fig. 2.

TABLE I. ACID-BASE RESPONSE TO TOTAL BODY PERFUSION FOR ONE HOUR AT VARIOUS FLOW RATES

FLOW RATE	pH INITIAL AND FINAL	pH CHANGE	BICARBONATE DEFICIT	LACTIC ACID INCREASE
0.4-0.8 L./M.²/min.	7.61 7.40	0.21	11.78	25.4
0.8-1.2 L./M.²/min.	7.58 7.42	0.16	6.37	16.11
1.2-1.6 L./M.²/min.	7.61 7.44	0.17	6.45	19.5
1.6-2.0 L./M.²/min.	7.43 7.39	0.04	4.25	17.2
2.0-2.6 L./M.²/min.	7.40 7.35	0.05	3.82	16.4

Differences in arteriovenous oxygen saturation were analyzed for 48 dogs. The rate of change in the A-V difference was also less beyond a perfusion rate of 1.2 L. per square meter per minute.*

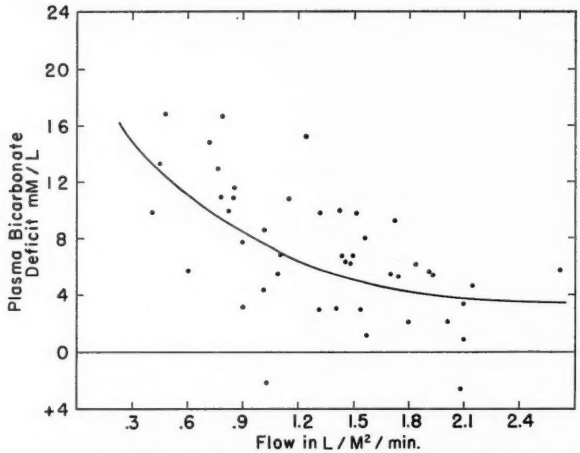

Fig. 2.—Determinations of the bicarbonate deficit in 48 dogs in Group B perfused for one hour. The solid line represents the sliding means for the individual measurements. Two conclusions derived from this data are worthy of emphasis. First, the fact that the plasma bicarbonate deficit changes very little above a flow rate of about 1.2 L./M.²/min. Second, the control dogs (Group A, text) undergoing one hour of anesthesia with the chest open and without extracorporeal perfusion had a mean plasma bicarbonate deficit of 4.92 mM./L. Thus, the animals perfused from the pump-oxygenator at a flow above 1.65 L./M.²/min. had a better maintenance of the acid-base balance than those animals (Group A, controls) perfused by their own heart and lungs under anesthesia with the chest open.

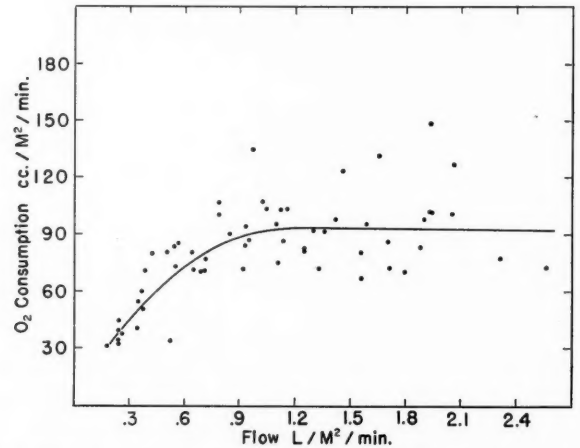

Fig. 3.—Total body oxygen consumption in dogs being perfused at varying flow rates (Group C, text). The solid line represents the sliding means of these measurements. Note the leveling off of this curve at a flow rate of approximately 1.2 L./M.²/min.

*The formula: Area = 11.2 $\sqrt[3]{\text{Wt.}^2}$ was used and the flow rate was then based on the body surface area obtained in this way.

Total body oxygen consumption at various perfusion rates in the 9 dogs in Group C is shown in Fig. 3. This data was obtained by multiplying the A-V saturation difference by the perfusion rate, the latter being determined by the venous return as described under "Methods."

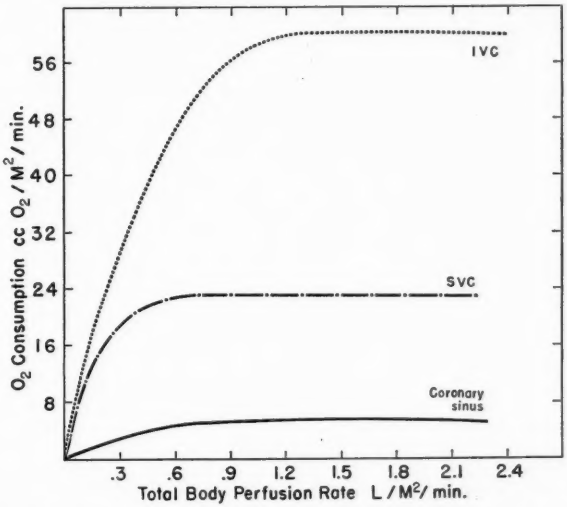

Fig. 4.—Fractional oxygen consumption in dogs being perfused at varying flow rates (Group C, text).

This graph (constructed from the sliding means of the individual determinations) indicates the O_2 consumption of the three major areas of the body. Note that the O_2 consumption of both the heart (coronary sinus system) and of the brain (superior caval system) are met by a total body flow rate of only 0.5 L./M.²/min. The needs of the tissues of the inferior caval drainage system are met by a minimum total body flow of about 1.2 L./M.²/min. (2.4 to 2.8 L./M.²/min. represents the resting cardiac output in the normal dog.)

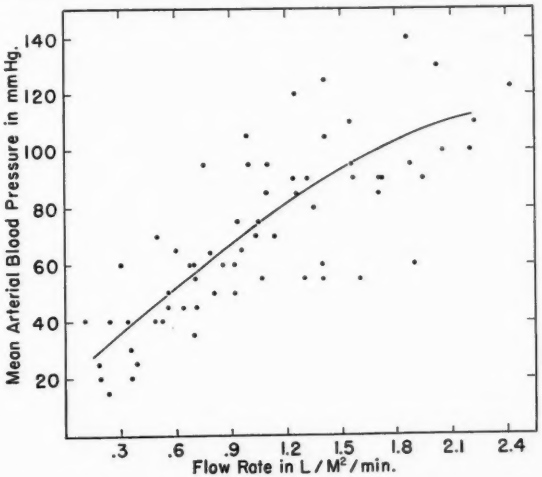

Fig. 5.—Mean arterial blood pressure in relationship to perfusion rate. Each canine determination is represented by single dot.

In 6 of these dogs, the oxygen consumption was further analyzed in relationship to the two caval systems and the coronary sinus. Fig. 4 is a graph constructed by plotting oxygen consumptions of the inferior caval, superior caval, and coronary sinus systems separately against the total body perfusion rate. As can be seen from this composite figure, the point at which the oxygen consumption levels off is not the same for each drainage area of the body. The oxygen consumption levels off at the lowest perfusion rate for the coronary sinus system and superior vena cava and at the highest perfusion rate for that part of the body drained by the inferior vena cava.

Fig. 5 is a graph showing the relationship between mean arterial blood pressure and perfusion rate. This is constructed from the data obtained from 13 dogs, each perfused at varying rates. These values agree well with those obtained in dogs perfused at a constant rate for one hour.

DISCUSSION

Our results confirm the opinion previously expressed[3] that pH changes alone do not accurately reflect the acid-base changes occurring during total cardiorespiratory by-pass. The fall in alkali reserve, or increasing bicarbonate deficit, represents a more precise measure of this change. From Table I it can be seen that the decrease in bicarbonate deficit was paralleled by a decrease in the accumulation of fixed acids as represented by the lactic acid values. It should be emphasized that these values were correct for temperature since both the animal and the blood perfused were kept at 39° C.

Fig. 2 demonstrates clearly that beyond a perfusion rate of 1.2 L. per square meter per minute the bicarbonate deficit, though still decreasing, does so very gradually and closely approaches the value of 4.92 mM/per liter for the control series. At perfusion rates above 1.65 L. per square meter per minute, the curve actually falls below this level indicating that from this point on the extracorporeal system was giving the dog a better perfusion than his own cardiorespiratory system under the conditions of the control experiment. This unique observation could well be due to the fact that the cardiac output falls when the chest is opened.[10] Most, if not all, anesthetic agents decrease cardiorespiratory efficiency.[11] Total oxygen consumption at various perfusion rates (Fig. 3) similarly shows a levelling off of the curve above a perfusion rate of 1.2 L. per square meter per minute. This observation is not due to inefficiency of the oxygenator system used in these experiments, since the arterial oxygen saturation did not fall below 95 per cent. Furthermore, the venous oxygen saturation above this perfusion rate approached normal resting values and finally exceeded it.

The close inverse relationship between the curves for bicarbonate deficit and oxygen consumption is very striking. Both curves plateau at a perfusion rate of 1.2 L. per square meter per minute. The normal resting or basal cardiac output for dogs is 2.4-2.8 L. per square meter per minute. It should also be pointed out that all animals were in a state of respiratory alkalosis with arterial carbon dioxide tensions ranging from 12 to 32 mm. Hg. This is in

part due to hyperventilation by the mechanical respirator and also due to the fact that pure oxygen was used in the oxygenator. The latter, being an open system, will allow carbon dioxide to escape freely from the blood.

The breakdown of total oxygen consumption values, as shown in Fig. 4 is interesting in that it indicates that the oxygen demands of the heart and of the upper part of the body, including the brain, are met at lower perfusion rates. Also, when the flow rates from the coronary sinus and superior caval catheters at the point where each levels off are added together a value approximating the azygos flow[12] is obtained. It should be noted that in Fig. 4 the abscissa represents the total venous return and not the return from each catheter separately.

From the standpoint of supplying oxygen to the tissues for by-pass periods up to 60 minute's duration, the optimun effect was obtained at perfusion rates of 1.2 L. per square meter per minute. Conversely, perfusion rates above this level did not favorably affect the development of metabolic acidosis significantly. A perfusion rate of 1.2 L. per square meter per minute results in a mean arterial pressure of 80 mm. Hg and this is considered to be an adequate level for this temporary interval.

It would appear, therefore, that this flow rate (1.2 L/M.^{2}/min.) represents the lowest level at which the whole body is being adequately perfused, or rather those tissues producing most of the acid metabolites under the conditions of the experiment are receiving their basic requirements for oxygen. This perfusion rate has been adopted clinically as the minimum quantity for acyanotic patients. In the cyanotic patients, a rate 15 to 25 per cent higher than this is currently recommended to offset losses from the gross perfusion rate due to pulmonary recirculation via the well-developed bronchial collateral system present in these patients.

Laboratory experience with the gravity siphon venous drainage has been so satisfactory that this system has been adopted as the method for withdrawing the caval blood for all clinical perfusions. In the operating room, a venous well (see insert Fig. 1) is placed in the venous line at about 50 cm. below the level of the right atrium. This gives a siphon suction of 50 cm. of blood. Venous blood collecting in this well is returned to the oxygenator by the venous pump. The level of blood in the well is allowed just to cover the lower end of the venous inflow line and thus splashing of blood into the well is minimized. Throughout the operation, venous pressures are monitored via a catheter in the median basilic vein of the arm with its tip passed up as far as the thoracic inlet. The central venous pressure recorded in this way during the period of by-pass has been found to fall uniformly an average of 5 cm. of water below the control or pre-occlusion level in the superior vena cava. Experimentally and clinically we have found that this method of collecting the venous return has been simpler and smoother than by direct pump suction and this observation is particularly true at higher perfusion rates. Venous flutter is avoided. Moreover, one can alter the perfusion rate during the period of by-pass simply by altering the pumping of the arterial head. It is a

simple matter to keep the level of venous blood in the well constant by altering similarly the venous pumping rate. Thus, this is essentially a self-balancing system inasmuch as it has been observed that venous return collected in this way accurately reflects the arterial inflow. The patient's blood volume with this system is kept constant throughout the period of by-pass. Any blood lost from the circuit, such as that from the coronary return, that is not recovered by the low pressure cardiotomy sucker system, is immediately observed as an equivalent fall in the level of the arterial blood in the helix reservoir. Such losses are replaced by transfusions into the oxygenator system.

The principle of gravity drainage has been used by others[13, 14] while Kirklin and his associates[15] recommend collection of venous blood in a negative pressure chamber.

Routinely, the electroencephalogram has been continuously monitored in all of our patients undergoing open cardiotomy. This method has been a sensitive and, therefore, a valuable index of cerebral well-being. One of the factors that has been found to influence the wave pattern unfavorably was congestion in the superior caval system such as may occur if the pliable caval wall is sucked into and occludes some or all of the catheter orifices. The free and unobstructed flow of venous blood out of the venae cavae obtained with the use of a gravity siphon system has obviated this effect.

SUMMARY

1. The relationship between plasma bicarbonate alterations and the perfusion rate during total cardiorespiratory by-pass for 60 minutes has been investigated.

2. These studies include fractional oxygen consumption determinations for the heart, the superior and the inferior caval drainage areas.

3. The developement of metabolic acidosis, as measured by the bicarbonate deficit, is inversely related to oxygen consumption.

4. At a perfusion rate of about 1.2 L. per square meter per minute (60 to 70 c.c/Kg./min. for a 10 Kg. dog), the oxygen consumption levels off, indicating that the basic tissue requirements for oxygen were being supplied and at this perfusion rate arterial pressures were at physiologic levels.

5. At a perfusion rate of 1.2 L. per square meter per minute, the plasma bicarbonate deficit approached the control value for animals subjected to 60 minutes of anesthesia with the chest open.

6. A simple method of gravity siphon venous drainage is described and its advantages for clinical use are discussed.

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(For Discussion, see page 587)

CORONARY PERFUSION AS AN AID TO THE OPEN REPAIR OF ATRIAL SEPTAL DEFECTS UNDER HYPOTHERMIA

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THE asphyxiated, manipulated, cold abnormal heart, therefore, is particularly prone to enter ventricular fibrillation at the time when attempt is being made to restore circulation.'' This statement by Swan, Virtue, Blount, and Kircher[1] epitomizes one of the major objections to the performance of open heart surgery during circulatory interruption under hypothermia. If the problem of cardiac arrhythmias could be solved, this technique would represent a simple and satisfactory method for certain intracardiac operations of brief duration. The present discussion concerns the clinical use of coronary perfusion as a method to prevent such arrhythmias.

Swan and associates report an incidence of ventricular fibrillation of 15 per cent in a series of 100 cases. Ten of these 15 instances occurred either during or immediately after the cardiac manipulation. Five of these patients resisted resuscitative efforts, and only 3 of the 15 patients were long-term survivors. Lewis, Taufic, Varco, and Niazi[2] indict ventricular fibrillation as the most disturbing complication of the repair of atrial septal defects during circulatory occlusion under hypothermia. Eleven of their 35 patients developed this complication. Nine of the 11 instances occurred during the actual operation upon the heart. Similar difficulty with ventricular arrhythmias has been reported by others.[3-5] Despite this high incidence of ventricular fibrillation, the human heart apparently has some natural resistance to the development of this arrhythmia. Many investigators have demonstrated the almost uniform occurrence of ventricular fibrillation in hypothermic dogs in which cardiac manipulation is attempted. Although the fibrillation is ordinarily intractable in dogs,[6, 7] Swan and associates[1] were able to resuscitate two thirds and Lewis and associates[2] 91 per cent of their patients.

A number of investigators have employed coronary perfusion in the experimental animal by introducing blood into the occluded aorta above the coronary ostia. Cookson and Costas-Durieux[8] employed an erythrocyte-gelatin solution, introduced under pressure, to maintain closure of the aortic valves and prevent air embolism. Shumway, Gliedman, and Lewis[9] and Riberi and associates[10] prolonged the period of circulatory interruption in dogs by perfusion of the coronary arteries with heparinized, arterialized blood. Jude, Fauteux, and

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Haroutunian[11] eliminated the occurrence of ventricular fibrillation in dogs with differential cardiac warming accomplished by a perfusion of warm arterialized blood through the coronary system during the period of circulatory interruption. Smith[12] demonstrated that coronary perfusion improves the electrocardiographic pattern in hypothermic dogs.

Sporadic clinical use of coronary perfusion has been reported. Cookson and Costas-Durieux[8] report one case in which it was used to prevent air embolism. Shumway, Gliedman, and Lewis[9] report 2 cases. Grow, Demong, and Hawes[13] employed coronary perfusion in 10 patients to effect closure of interventricular septal defects. Seven of the 10 patients survived. Bahnson[14] employed the method to close an atrial septal defect associated with anomalous venous return in a 7-year-old boy.

The present discussion concerns the results of operation in 12 consecutive patients operated upon for isolated ostium secundum atrial septal defect by the open technique under hypothermia. In one half of the patients, the coronary arterial system was perfused during the period of circulatory interruption with heparinized, arterialized blood.

METHOD

After anesthesia was induced, cooling was initiated by packing the patient in ice bags or by wrapping him in a refrigerating blanket containing cold, circulating brine. Cooling was stopped when the patient's temperature was lowered to 32° C. Temperatures drifted downward a degree or two by the time of caval occlusion. The electrocardiogram, arterial pressure, and body temperature were recorded continuously.

Blood for perfusion of the coronaries was drawn from the venous system of compatible donors immediately before operation. To obtain the highest possible oxygen saturation, the donor's arm was warmed in a water bath at 45° C. while he breathed 100 per cent oxygen. Blood was collected in siliconized bottles containing 17 mg. of sodium heparin dissolved in 10 ml. of normal saline. The blood was stored in a water bath at 35° C. until used. Patients were prepared for circulatory interruption by exposure of the heart by a bilateral sternum-splitting thoracotomy in the fourth interspace. Occluding tapes were placed around the superior and inferior venae cavae as described by Swan and Zeavin.[15] In the first 6 patients in this series, venae cavae were occluded and the heart was permitted approximately 15 seconds to empty of blood. A noncrushing occlusion clamp was then placed across the aorta and pulmonary artery in such manner that the coronary ostia were occluded. In the second group of 6 patients, the occlusion clamp was placed as high above the root of the aorta as possible, close to the origin of the innominate artery. A needle, varying in size from No. 20 to No. 15, was inserted into the aorta between the clamp and the coronary ostia. The needle had previously been connected to the bottle containing the heparinized, arterialized blood. Perfusion was assisted by increasing the air pressure in the bottle by means of a hand pump. The coronaries were perfused at a rate of 3.0 ml. per kilogram of body

weight per minute, except for one patient who was perfused at the rate of 1.5 ml. per kilogram of body weight per minute. The right atrium was then opened and the atrial septal defect repaired by suture under direct vision. In those patients in whom coronary perfusion was employed, there was a constant flow

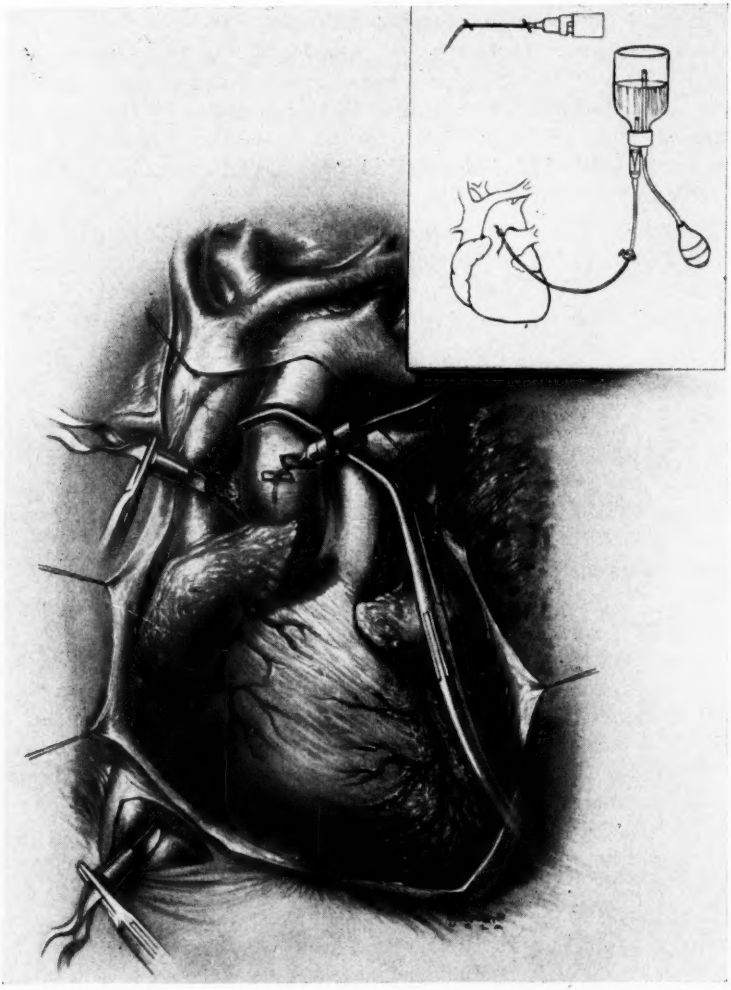

Fig. 1.—Technique of coronary perfusion used in this study.

of blood from the coronary sinus ostium. This blood was easily aspirated and did not represent a significant obstruction to vision within the heart. The left side of the heart was filled with saline before the last suture was placed in the septal defect. The right side of the heart was filled in a similar manner and a

nonerushing occlusion clamp was used to close the right atrial wall temporarily. The caval occlusion was then released, and the atrial wall was closed with a continuous silk suture (Fig. 1).

RESULTS

The first 6 patients, who were operated upon without coronary perfusion, survived the operative procedure and had an uncomplicated postoperative course. However, during and immediately following circulatory occlusion, there was an alarming incidence of complications, suggesting that the myocardium was undergoing a severe physiologic insult. In every patient, the myocardium became deeply cyanotic during the 6- to 8-minute occlusion period. Four of the 6 patients developed poor myocardial tone with dilatation of the heart following release of the caval occlusion. All 6 patients required one or more minutes of manual intermittent cardiac compression before the heart was able to maintain circulation. Four of the 6 patients developed severe arrhythmias; 2 developed ventricular fibrillation. In these last 2 patients, normal rhythm was easily restored by cardiac compression followed by electric shock therapy. These complications are summarized in Table IA. In each instance following release of the venae cavae, the return of arterial pressure and adequate peripheral tissue perfusion was a gradual process occurring over a period of several minutes.

TABLE IA. HYPOTHERMIA WITHOUT CORONARY PERFUSION

AGE (YEARS)	ARRHYTHMIA	FIBRILLATION	POOR TONE	CYANOSIS	MASSAGE
7	+	+	+	+	+
7	0	0	0	+	+
4	0	0	0	+	+
10	+	+	+	+	+
3/12	+	0	+	+	+
3	+	0	+	+	+

In contrast with the preceding patients, those in whom coronary perfusion was done had a remarkably uncomplicated course. Five of the 6 patients in this group were entirely free of the cardiac abnormalities shown by the previous group. The sixth patient was a 47-year-old woman whose coronary system was perfused at half the usual flow rate (1.5 ml. instead of 3.0 ml. per kilogram of body weight per minute). This patient developed poor myocardial tone following release of circulatory occlusion. It was necessary to massage the heart for a period of several minutes and to give 2.0 ml. of 10 per cent calcium chloride to improve the cardiac tone. The results from this group of patients are summarized in Table IB. Instead of showing progressive cardiac slowing during the occlusion period, the heart continued to beat regularly and the myocardium remained a normal pink in color. Continuous oscillographic records demonstrated that, in this group of patients, systemic arterial pressure returned to normal levels within 4 to 5 heartbeats following the restoration of circulation. Fig. 2 illustrates this rapid recovery in a 5-year-old girl who had an atrial defect repaired during a 5-minute period of circulatory occlusion.

As in the first group of patients, all 6 patients who had coronary perfusion did well following surgery.

TABLE IB. HYPOTHERMIA WITH CORONARY PERFUSION

AGE (YEARS)	ARRHYTHMIA	FIBRILLATION	POOR TONE	CYANOSIS	MASSAGE
7	C	0	0	0	0
3	0	0	0	0	0
47*	0	C	+	0	+
2	0	0	0	0	0
5	0	0	0	0	0
4	0	0	0	0	0

*The coronary system was perfused at half the usual flow ratio in this patient (1.5 ml. instead of 3.0 ml./Kg./body weight/min.).

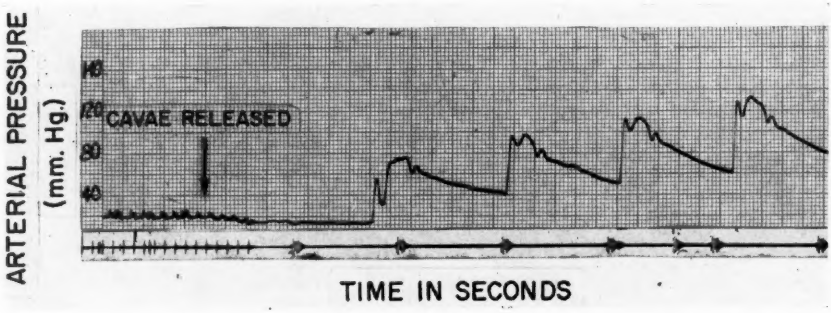

Fig. 2.—Continuous arterial pressure tracing showing prompt return of preocclusion pressure after caval release.

DISCUSSION

The results reported here strongly suggest that a "metabolic debt" develops in the myocardium during the period of circulatory occlusion. This debt, rather than hypothermia itself, appears a more logical explanation of ventricular arrhythmias occurring with this technique. The results of perfusing the coronary system with arterialized blood have been so satisfactory that no attempt has been made to evaluate procaine block of the S-A node,[16] respiratory alkalosis,[7] carbon dioxide administration,[17] or drugs[18, 19] in the prevention of arrhythmias. Perhaps each of these modalities is a factor in preventing ventricular fibrillation by making the myocardium less susceptible to low partial pressures of oxygen or increased concentrations of tissue metabolites. The prevention of myocardial hypoxia and metabolite accumulation by coronary perfusion would appear a more direct and logical approach to the problem.

The results in the patients given coronary perfusion fall short of being perfect only because of the appearance of poor myocardial tone in the 47-year-old patient. A likely explanation of the poor myocardial tone in this patient is the fact that the coronary system was perfused at 1.5 ml. per kilogram of body weight per minute, a rate which is half that employed in other patients in this series. The No. 15 needle introduced into the aorta was inadequate in size to permit the flow of the desired amount of blood.

The nonperfused and perfused groups of patients are entirely comparable with a single exception. With increasing experience, the surgeons required a shorter operating time within the heart. The first group (nonperfused) had

an average occlusion time of 7 minutes (range, 6 to 8 minutes). The second group (perfused) averaged 5 minutes of occlusion (range, 3 to 6.2 minutes). The myocardial complications in the first group cannot be attributed to the longer average time of occlusion, since these complications usually had their onset within the first 3 minutes of occlusion.

The perfusion rate of 3.0 ml. per kilogram of body weight per minute was obtained empirically. Normal coronary flow was assumed to be 4.6 ml. per kilogram of body weight per minute.[20] Since the patients in this series were cooled from 37° to 30° C., and since body metabolism is decreased approximately 5 per cent per degree centigrade reduction of body temperature,[21] the heart might be expected to have a 35 per cent reduction in metabolic requirement. Therefore, 65 per cent of the normal coronary flow, approximately 3.0 ml. per kilogram of body weight per minute, was chosen. The data of Edwards and associates[22] demonstrate that reduction of myocardial metabolism during hypothermia is relatively less than the reduction in the rest of the body. Therefore, perhaps somewhat higher perfusion rates than were employed in these cases would be desirable.

Although coronary perfusion reduces the hazard of open heart surgery under hypothermia, the same fundamental criticism of the hypothermia technique still remains, i.e., limitation of operating time within the heart. Occlusion of the circulation for periods longer than 10 minutes is likely to produce cerebral damage. This study was not undertaken in an attempt to extend the occlusion time beyond the previously established limits of safety. Rather, the effort was to increase the safety of an occlusion time of limited duration. The method does not give sufficient operating time for repair of defects of the ostium primum or atrioventricularis communis types. A logical extension of the rationale and results of this study would be that all intracardiac operations, even of brief duration, should be performed during circulatory by-pass on a heart-lung machine. That is, if myocardial physiology is better when the heart is perfused with arterialized blood, then total body physiology will also be improved by perfusion. Extracorporeal circulation has been reserved in this clinic for the performance of intracardiac operations of longer duration. The morbidity and mortality associated with the use of a heart-lung machine at the present time exceed the danger of the open technique under hypothermia. Over a 4-year period, the mortality in this clinic for the repair of ostium secundum septal defects by atrioseptopexy, Gross well, and hypothermia techniques is 4 per cent. Of the 2 deaths in 50 patients, one occurred after the induction of anesthesia. With open operation under hypothermia, there has been no mortality. Although the open technique with the pump-oxygenator may eventually prove the best method, we believe that the technique herein described represents the safest and most effective method currently available.

SUMMARY

Twelve patients underwent direct vision cardiac surgery during circulatory interruption under hypothermia. Six were operated upon with this technique

alone. There was a high incidence of serious cardiac arrhythmias, myocardial cyanosis, and loss of muscle tone. In the second group of 6 patients, the coronary arterial system was perfused with heparinized, arterialized blood during the period of circulatory interruption. The only myocardial complication occurring in this group of patients was poor heart tone in one patient whose coronary system was perfused at an inadequate rate.

Although all 12 patients survived and did well following surgery, the reduction in complications in the perfused group suggests that coronary perfusion greatly enhances the safety of open heart surgery under hypothermia.

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Discussion

(Papers by Giannelli [page 563], Paneth [page 570], and Maloney [page 580] and their associates)

DR. CLARENCE DENNIS, Brooklyn, N. Y.—I wish to comment on the paper by Mr. Paneth. My associates and I made a report on the metabolic changes with regard to total body perfusion, in the 1952 Surgical Forum of the American College of Surgeons; that was presented by Dr. Dwight Spreng. At that time, we perfused at what was estimated to be the total normal cardiac output of the animal in question, and it seemed that, no matter what we did, there was a gradual accumulation of fixed acid, and that we were unable to make any changes that would lead to disappearance of this accumulation. My reason for speaking now, was to indicate that even when one gets a much larger turnover than is normal for the animal, there is still an accumulation of fixed acid.

In the first patient whom a group of us perfused in Minneapolis in 1951, the flow rate went as high as 220 c.c. per kilogram per minute. Even under these circumstances there was some accumulation of fixed acid.

DR. ETHAN FLAGG BUTLER, Elmira, N. Y.—I crave permission at this time to repeat a legend, a legend of 40 years ago. I am prompted by two considerations, first, the very many excellent reports on practical cardiovascular surgery; second, the fact that this is the 40th anniversary of the founding of this Association, which may well be described as the vigorous, dynamic, manifestation of a man's faith.

Willy Meyer had faith that the prohibitive morbidity and mortality attendant upon thoracic trauma and thoracic operations could be brought under control. With others who shared that faith he urged the organization of a group to study all aspects of thoracic surgery. But there were men of lesser faith who tried to dissuade him. "Willy Meyer," they said, "Don't form that society; you are doomed to disappointment. You have only a few 'topics' to talk about. In 2 or 3 years everything will have been said and your society will die for lack of interest. Your only topics are empyema, aneurysms, bronchiectasis, tumors of the chest wall. It isn't likely there ever will be any practical surgery of the esophagus; surgical treatment for consumption is a fad, and everybody knows that you can't operate on the heart."

DR. PAUL DE CAMP, New Orleans, La.—I think the group from Pennsylvania are to be congratulated on tackling this problem. It is never very glamorous to try to find out what the trouble is with anything. We certainly have felt that with reports coming out of a mortality rate that, even in the better groups of cases, is running in the order of magnitude of 25 per cent to 35 per cent or higher, perhaps it is not wise for us at this stage to blame the patient, which is what we usually do when things are not going well and we don't know why.

The first thing I would like to point out is that the rate of flow of oxygen in the blood oxygenator is not always necessarily better because it is faster, and the ratio of 8 to 1 or 10 to 1, with different types of oxygenator, may not be necessary. This was graphically brought to our attention recently by a report from a group using a type of bubble disperser which was similar to the one we had been using and, at comparable blood flow rates, we had found that a 5 to 1 ratio had given us complete oxygen saturation with tension as high as 550, and yet the report from the other group using it at 10 L. per minute said they were getting unsatisfactory oxygenation. It must be borne in mind that if large oxygen flow rates are used it may sweep the blood through the oxygenator so fast that the time of contact of oxygen is limited and therefore under certain circumstances a lower flow rate may be better.

We have also been impressed with the value of a very slow outflow tract at some point, and I am delighted to see that they have found that the insertion of a reservoir is helpful, because in the oxygenator which Dr. Hyman has developed in New Orleans that is an integral part of the oxygenator.

We too have been concerned about antifoam. Antifoam, for those who may not know the details, was originally designed for commercial purposes and has never been changed for medical purposes. Originally a clear oil, which had antifoaming properties only in an oily solution, which, when combined with silica developed antifoaming properties in an aqueous solution. Produced both as a grease and as a spray, in either case, droplets may form and it is possible that these may be part of the difficulty. We have injected it intravenously and also into the aortic arch in dogs, and have not been able under those experimental conditions to reproduce difficulties. It is possible to remove the silica and, after it has been removed, the remaining residual oil retains its properties of antifoaming in an aqueous solution. This is something which the Dow Corning people found out but ignored, because for commercial purposes it made no difference whether the silica was there or not and, of course, it is very expensive to remove it. Dr. Hyman found it out independently and felt it might be of some medical significance. The results of these reported experimental studies suggest that particulate matter may be present in the blood as it leaves the oxygenator.

I think it would be very interesting if the group at Pennsylvania would try removing the silica and then testing it again to see if, with the silica absent, the animals get into trouble.

The only thing I would like to point out is that the antifoam will penetrate Tygon plastic, so when it is used on that type of surface there is probably less danger of it being swept off, particularly if time is permitted for penetration to take place. However, if used on metal it is much more apt to be washed off and get into the solution.

DR. JOE D. MORRIS, Ann Arbor, Mich.—I should like to confirm Dr. Gianelli's point about the value of the vertical large mass reservoir. We have come to the same conclusion during the development of a clinically successful oxygenator at the University of Michigan. The vertical bubble oxygenator we have used (slide) is similar to that described by Lewis and Shumway as well as by Nelson and his associates. The oxygenating column is a vertical cylinder telescoped into a cylinder of greater diameter which serves as a defoaming and collecting reservoir. The initial use of this device in the laboratory was followed frequently by evidence of neurologic damage in the perfused animal which ranged from spasticity to coma. Histologic examination of the brains of the dogs exhibiting neurologic deficits revealed scattered focal changes which were compatible with emboli, although no specific embolic agent could be identified. Fibrin and air were considered possibilities. At this time, small volumes of blood were being used to prime the oxygenator. The use of larger priming volumes of 1,000 to 1,500 c.c. of blood eliminated neurologic complications. The larger priming volume elevated the depth of the column of blood in the defoaming and collecting reservoir to approximately 6 inches. After successful perfusions, a thin scum of fibrin and enmeshed white blood cells was apparent on the wall of the reservoir at the level of the top of the blood column. It seemed that this fibrin precipitate had been floated out by the large vertical blood reservoir and prevented from entering the arterial system. Fibrin precipitation appeared to be correlated directly with the duration of perfusion and volume of foam accumulating in the defoaming reservoir. Later application of a woven nylon bonnet, impregnated with antifoam on top of the oxygenating cylinder, reduced foaming to a minimum and nearly eliminated fibrin precipitation. We believe that one of the necessary features of the successful bubble oxygenator is a large reservoir column of blood which serves as a flotation barrier to precipitated fibrin and air bubbles and thereby prevents the entry of either into the arterial system.

DR. GEORGE H. A. CLOWES, JR., Cleveland, Ohio—I should like to make a comment on the metabolic phenomena found during total perfusion, which Mr. Paneth has presented so nicely. At the same time I should like to take this opportunity to bring you up to date on the membrane oxygenator which we presented before this Association last year.

With regard to the matter of metabolic acidosis, it appears that this is a matter of inadequate oxygen supply to certain tissues in the body. Unless this is compensated by a relative respiratory alkylosis at a time state of acidosis will exist and the arterial pH will fall. If one can assume that an oxygenator is not introducing particulate or gaseous emboli to damage the brain, it is oxygen lack and the attendant acidosis which matters primarily and not the flow rate per se in causing mortality.

(slide) By way of illustration, let me quote four series of animals totally perfused for one hour with the membrane oxygenator as you see it here. It now holds only as much blood as other types and has been used to support circulation in animals up to 4 hours with survival. Clinically we have employed it 5 times. In only one instance did the patient fail to recover from cardiotomy, due to a technical error.

(slide) This is the chart of an animal typical of the first group in which total perfusion was carried on for one hour with a relatively high flow rate (85 c.c./Kg./min.) and an oxygenator capable of furnishing adequate oxygenation. You will notice little change except that the venous oxygen content fell slightly. Brain waves and electrocardiogram changed little. All but one of these dogs survived.

(slide) Compare this with the group which were perfused at low flow rates with adequate oxygenation. There was some slight depression of the brain waves. The venous oxygen content fell showing that the average oxygen tension in the tissues of the body was very low. This resulted in a marked use of lactic acid due to anaerobic metabolic activity. The arterial pH changed but little because of a fall in CO_2 and a relative respiratory alkalosis. Although these dogs were slow to wake up, the majority of them recovered.

In 2 groups of animals, perfused with oxygenators capable of furnishing only one half the required oxygen, nearly all died. It did not make any difference whether flow rate was high or low. Severe electroencephalographic depression occurred, probably due to the intense acidosis, both metabolic and respiratory, which took place under these conditions.

In other words, as Mr. Paneth has shown, below a certain rate of perfusion a shock state exists in which some of the tissues receive inadequate supplies of oxygen. This, in turn, results in metabolic acidosis which must be compensated for by blowing of CO_2 or irreparable brain damage and death will result.

MR. MATTHIAS PANETH, London, England (Closing).—Concerning Dr. Dennis' remarks on acidosis, we did not suggest at any stage that you could get away without any fixed acids whatsoever. I think you always get a certain amount simply because you perform an operation. If you could perfuse at a flow rate well above normal, not at rest, but at the normal cardiac output, theoretically you would get no metabolic acidosis; but this would mean a large minute volume and under the conditions of anesthesia I think the animal's vascular state would not safely support such a volume of blood.

We have shown in the course of these experiments, by serial estimations during the perfusion, that there is a linear relationship between the accumulation of fixed acids and the duration of perfusion. Moreover, the oxygen uptake remains constant throughout a period of one hour.

I should like to close by saying how grateful I am to the Association for their kindness in granting me this Fellowship, and in particular to Dr. Lillehei and his group who have given me every encouragement and taught me all I know about perfusion techniques.

ALTERATIONS IN RENAL HEMODYNAMICS DURING CONTROLLED EXTRACORPOREAL CIRCULATION IN THE SURGICAL TREATMENT OF AORTIC ANEURYSM

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RESECTIONAL therapy of thoracic aortic aneurysms presents challenging physiologic problems concerning control of circulation during temporary occlusion of the aorta. Methods which have been used to prevent ischemic damage to sensitive areas during the occlusive period have employed divergent physiologic principles. The effectiveness of general body hypothermia in the prevention of spinal cord ischemia has been clearly demonstrated for resection of aneurysms located in the descending thoracic aorta.[2] A second effective method in preventing renal and spinal cord damage, and one which also allows decompression of the proximal aorta, is the temporary vascular shunt.[6] Side branches can be attached to the carotid arteries to maintain cerebral circulation. Thus, large caliber shunts may be sutured to the aorta above and below the area to be isolated, making feasible resection of portions of the aortic arch.[5] A third method, which has recently been adopted, employs a pump to control extracorporeal circulation during the occlusive period.[4] This technique offers two outstanding advantages: simplicity and continuous control.

Two methods of controlled extracorporeal circulation were used for resection of thoracic aneurysms. For aortic by-pass to facilitate resection of aneurysms arising in the descending thoracic aorta, a proximal catheter was placed either in the left atrium or left subclavian artery and a distal catheter in one common femoral artery for return of blood (Fig. 1). When cardiopulmonary by-pass was necessary during the resection of aneurysms of the aortic arch, a pump-oxygenator was employed.[3] With this method, venous blood was removed from the venae cavae, pumped through a modified DeWall-Lillehei oxygenator, and returned through a femoral catheter (Fig. 2).

The purpose of this study was to determine the optimum rate of flow for controlled extracorporeal circulation in aortic surgery. Although it is desirable to measure spinal cord activity as a reflection of the adequacy of extracorporeal circulation, methods for this purpose are not readily available. It is possible, however, to estimate renal blood flow and glomerular filtration rate and use these measurements as evidence of the effectiveness of the perfusion blood flow.

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METHODS

Two groups of patients were used in the study; one requiring aortic pump by-pass for aneurysms of the descending thoracic aorta, and the other cardiopulmonary by-pass for aneurysms of the arch or cardiac operations. In the former group, studies were performed on 13 patients in whom temporary extracorporeal circulation was used during resection of aneurysms of the descending thoracic aorta. A proximal plastic catheter was placed in the left atrium through the atrial appendage and connected to a length of $\frac{3}{16}$ inch polyvinyl tubing. A distal catheter was threaded proximally through an arteriotomy in one common femoral artery with a Sigmamotor pump interposed to control the rate of flow through the circuit. In the second group, consisting of 11 patients, cardiopulmonary by-pass was employed, using a bubble diffusion oxygenator of the DeWall-Lillehei type.

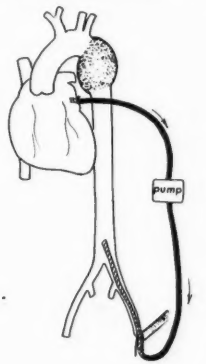

Fig. 1.

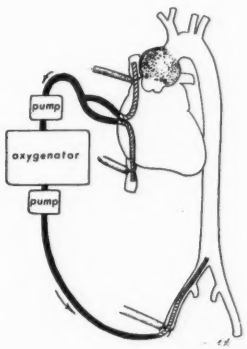

Fig. 2.

Fig. 1.—Circuit diagram of extracorporeal circulation as used during resectional therapy of aneurysms located in the descending thoracic aorta. Blood was pumped from a catheter placed in the left atrium to the distal aorta by way of a second catheter placed in one common femoral artery.

Fig. 2.—Circuit diagram of extracorporeal circulation as used for cardiopulmonary by-pass with the pump-oxygenator. When occlusion of the carotid arteries was necessary, an additional pump was added to perfuse these vessels.

Mean blood pressure during the dependent period of aortic or cardiopulmonary by-pass was determined by direct measurement, using a water manometer attached to a 15-gauge needle inserted in the distal aorta. All other mean blood pressures were derived from auscultatory pressures by adding one third the pulse pressure to the diastolic pressure. Inulin and para-aminohippurate clearances were used to estimate glomerular filtration rate and renal plasma flow, respectively, employing techniques previously described.[7] Renal blood flow was calculated from renal plasma flow with the hematocrit.

Flow rates of the Sigmamotor pumps were carefully calibrated just prior to operation in each case. In the aortic by-pass series, the flow rates were low and somewhat variable in the first few patients, but later approached 1,200 to 1,400 c.c. per minute. This followed our estimate that 20 c.c. per kilogram of body weight probably represented the most satisfactory rate of flow. In actual

TABLE I. RENAL HEMODYNAMICS DURING AORTIC BY-PASS WITH A PUMP

NO.	PATIENT	AGE	RACE SEX	OCCLUSION TIME (MINUTES)	MEAN PUMP FLOW RATE (C.C./MIN.)	MEAN BLOOD PRESSURE (MM.Hg)						RENAL BLOOD FLOW (C.C./MIN.)					GLOMERULAR FILTRATION RATE (C.C./MIN.)				
								P													
						C*	O_1	UPPER	LOWER	O_2	F	C	O_1	P	O_2	F	C	O_1	P	O_2	F
1	R. B.	43	WM	50	525	89	—	—	—	—	83	1,340	—	—	—	907	127	—	—	—	115
2	M. L.	44	WM	43	1,200	93	84	106	44	85	93	1,356	1,494	30	1,806	1,822	143	136	3	88	160
3	J. S.	67	WF	35	650	93	80	110	28	—	88	500	—	—	—	370	62	—	—	—	45
4	J. B.	42	WM	57	360	106	87	100	—	—	95	1,200	—	—	—	1,097	79	—	—	—	103
5	S. H.	52	WM	45	400	97	—	—	—	—	92	653	—	—	—	567	98	—	—	—	72
6	O. B.	61	CM	45	825	123	129	120	41	116	93	917	46	28	1,146	937	156	9	3	93	105
7	A. H.	43	WF	35	1,300	107	127	124	37	112	—	789	587	11	1,103	—	115	52	4	62	—
8	B. V.	62	WF	17	1,200	88	102	92	45	100	—	800	432	393	256	—	68	49	11	10	—
9	B. M.	57	WM	70	400	110	100	112	30	87	104	898	409	0	240	—	91	54	0	28	51
10	E. G.	66	WM	46	1,250	114	116	126	43	118	93	538	977	30	598	829	84	86	2	55	66
11	O. G.	64	WM	45	1,240	110	118	139	48	—	119	348	668	32	—	625	49	47	2	—	71
12	B. H.	61	WF	27	1,250	126	118	133	56	128	—	255	365	49	495	—	30	40	10	38	—
13	C. S.	47	WM	60	1,000	120	105	123	28	60	—	1,698	2,793	0	2,973	—	134	114	0	96	—
Mean		55		44	892	106	106	117	40	101	96	869	863	64	1,077	894	95	65	4	59	88
Per cent of control							100	110	38	95	91		99	7	124	103		68	4	62	93
Mean per cent of control							98	108	37	92	93		108	10	117	111		77	7	61	92

Key to abbreviations: C = Before operation. O_1 = During thoracotomy before occlusion of the aorta. P = During occlusion of the aorta. O_2 = During thoracotomy after occlusion of the aorta. F = Following operation.

practice, it is usually necessary to make adjustments in the rate of flow from time to time to maintain a proximal aortic pressure 10 to 20 mm. Hg above the preoperative level. The flow rate for the pump-oxygenator was generally 35 c.c. per kilogram of body weight, except when operational factors forced a slight reduction.

Observations of blood pressure, renal blood flow, and glomerular filtration rate were made before operation, during anesthesia with thoracotomy, during the period of extracorporeal circulation, and following re-establishment of normal circulation.

RESULTS

Group 1, Aortic By-pass.—In Table I are compiled the detailed observations on patients having resection of aneurysms of the descending thoracic aorta with the pump by-pass. The period of aortic cross-clamping ranged from 17 to 70 minutes and averaged 44 minutes. The flow rates varied from 200 to 1,400 c.c. per minute and averaged 892. Mean blood pressure before operation averaged 106 mm. Hg, and was not altered by anesthesia and thoracotomy. When the distal aortic arch was occluded, the mean pressure in the right arm rose to 117 mm. Hg, ranging from 92 to 139 mm. Hg. Pressure mm. Hg. After release of the aortic clamps and discontinuance of the pump, in the distal aortic segment averaged 40 mm. Hg, and ranged from 28 to 56 the mean blood pressure was 101 mm. Hg for the group.

Renal blood flow and glomerular filtration rates generally correlated well with the blood pressure. Anesthesia and thoracotomy had little effect on average renal blood flow, although glomerular filtration rate fell to 77 per cent of control. During the period of circulatory support with the pump by-pass, the mean per cent of control in renal blood flow fell to 10 and in glomerular filtration rate to 7 for this group. In 2 patients having the lowest pressures in the lower aorta, 28 mm. Hg, there was no measurable renal function. In the patient with the highest distal aortic pressure, 56 mm. Hg, renal blood flow was 49 c.c. per minute or 19 per cent of control. In the patient, however, with the second highest distal aortic pressure, 45 mm. Hg, the renal blood flow was the highest, 393 c.c. per minute. In the cases of the lowest aortic pressures, the glomerular filtration rate was zero, and in the 2 patients with the highest pressures, the rate was 10 and 11 c.c. per minute, respectively. Immediately after release of the occluding clamps, renal blood flow generally returned to normal, but glomerular filtration remained somewhat depressed (61 per cent). This function, however, returned toward normal during the latter postoperative period.

Group 2, Cardiopulmonary By-pass.—The data derived from studies on patients having cardiopulmonary by-pass with the pump-oxygenator are presented in Table II. With this procedure there is no proximal and distal pressure differential since the entire body is perfused. The mean pressure in the aorta during by-pass averaged 44 mm. Hg and ranged from 35 to 52 mm. Hg. Hence, measurable renal function was generally greater than that found with aortic pump by-pass. Renal blood flow averaged 24 per cent of control and

TABLE II. RENAL HEMODYNAMICS DURING CARDIOPULMONARY BY-PASS WITH A PUMP OXYGENATOR

NO.	PATIENT	AGE	RACE SEX	DEPENDENT TIME (MINUTES)	MEAN PUMP FLOW RATE (C.C./MIN.)	MEAN BLOOD PRESSURE (MM. HG)					RENAL BLOOD FLOW (C.C./MIN.)					GLOMERULAR FILTRATION RATE (C.C./MIN.)				
						C*	O_1	P	O_2	F	C	O_1	P	O_2	F	C	O_1	P	O_2	F
1	J. A.	14	WM	12	1,250	67	73	—	75	72	530	226	165	44	291	64	28	21	4	45
2	B. G.	13	WF	8	1,300	92	94	—	108	80	573	404	0	805	496	68	44	0	61	63
3	W. H.	50	WM	31	2,500	83	—	—	—	83	1,076	—	—	—	821	102	—	—	—	115
4	L. H.	42	WF	7	2,170	70	92	35	88	88	421	404	58	477	426	57	60	9	43	65
5	M. H.	42	WF	30	2,135	93	94	—	34	76	873	676	117	83	277	77	84	14	14	23
6	J. I.	27	CF	9	1,600	75	65	—	67	—	517	432	—	219	—	59	56	—	28	—
7	P. J.	11	WF	15	1,000	97	83	—	82	75	510	375	309	200	337	45	43	39	21	41
8	M. M.	49	CM	45	2,200	103	103	50	120	—	570	511	33	191	—	151	66	5	17	—
9	B. M.	56	WM	45	1,650	96	77	52	89	—	876	137	402	873	—	99	14	39	51	—
10	E. P.	27	WF	22	1,650	71	88	37	62	—	842	610	185	344	—	61	69	19	36	—
11	J. S.	11	WF	6	1,100	86	129	—	88	98	600	424	138	464	527	67	57	22	51	79
Mean		31		21	1,687	85	90	44	81	82	672	420	156	370	454	77	52	19	33	62
Per cent of control							106	52	95	96		63	23	55	68		68	25	43	81
Mean per cent of control							107	51	97	99		69	24	60	72		77	29	48	90

Key to abbreviations: C = Before operation.
O_1 = During thoracotomy before cardiopulmonary by-pass.
P = During cardiopulmonary by-pass.
O_2 = During thoracotomy after cardiopulmonary by-pass.
F = Following operation.

glomerular filtration rate 29 per cent. After resumption of normal circulation, renal blood flow and glomerular filtration rate returned to 72 per cent and 80 per cent of control values, respectively.

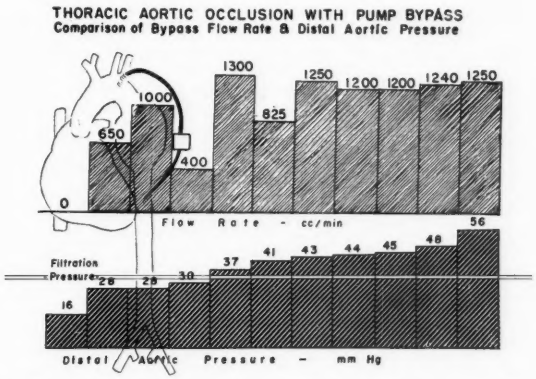

Fig. 3.—The effect of by-pass flow rate on distal aortic pressure. In one case, no by-pass was employed and collateral circulation was able to maintain a mean blood pressure of only 16 mm. Hg. It was generally necessary to pump at least 1,200 c.c. per minute to sustain a functional distal aortic pressure.

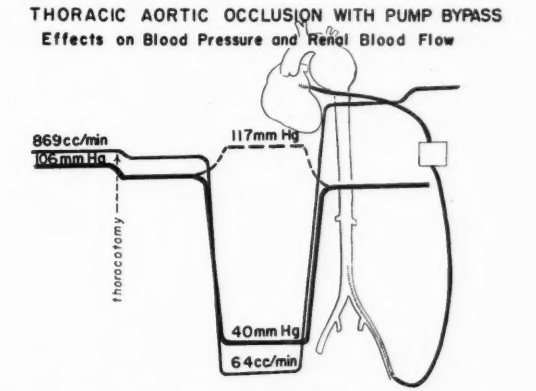

Fig. 4.—Relation of mean blood pressure in the lower aorta compared to renal blood flow during resection of aneurysms located in the descending thoracic aorta. The average mean blood pressure above the occlusion rose to 117 mm. Hg in association with an average pump flow rate of 869 c.c. per minute. This was in sharp contrast to a single case without by-pass in which the proximal aortic pressure rose 30 mm. Hg and distal pressure fell to a functionless 16 mm. Hg.

DISCUSSION

Group 1, Aortic By-pass.—The question of optimum pump flow rates during resectional procedures for aneurysms of the descending thoracic aorta appears at least partially answered by this study. To obtain with reasonable assurance a functional pressure in the distal aortic segment, it is necessary to use a flow rate of at least 20 c.c. per kilogram of body weight (Fig. 3). When flow rates less than this are used, lower aortic blood pressure is usually below

the filtration level. Although the mean blood pressure in the distal aortic segment during pump by-pass averaged only 40 mm. Hg, such low pressures were sufficient to produce measurable renal blood flow ranging from 2 per cent to 49 per cent of control (Fig. 4). When distal aortic pressure fell below the filtration level, no measurable function was observed. Previous studies have

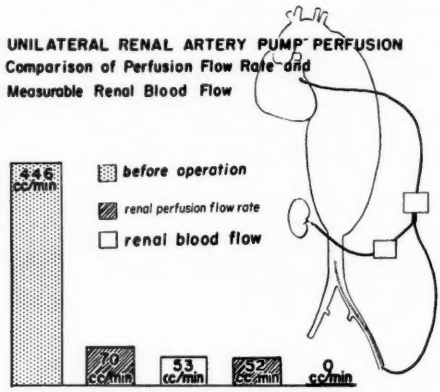

Fig. 5.—Comparison of perfusion flow rate and measurable renal blood flow as determined by renal clearance observations. In this case one renal artery was perfused during resection of a thoracoabdominal aneurysm involving both renal arteries. The renal blood flow as determined by clearance techniques correlated closely with a perfusion rate of 70 c.c. per minute, but no function was measurable when the perfusion rate was reduced to 53 c.c. per minute.

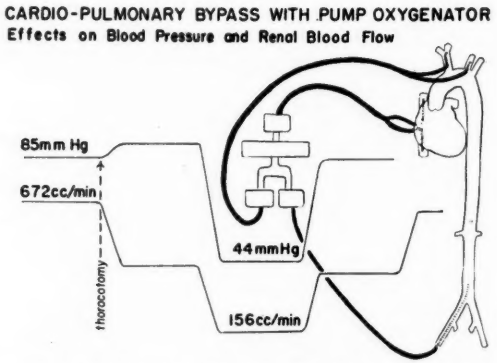

Fig. 6.—Effects of cardiopulmonary by-pass with the pump-oxygenator on mean blood pressure and renal blood flow. Thoracotomy produced a marked reduction in renal function in this group of patients. A mean blood pressure of 44 mm. Hg during cardiopulmonary by-pass afforded sufficient pressure to sustain a renal blood flow of 156 c.c. per minute.

shown that without any type of by-pass, collateral circulation will produce a blood pressure below the point of aortic occlusion of 12 to 30 mm. Hg.[8, 9] Hence, the pump by-pass probably adds little protection from ischemic damage to distal vascular beds if the flow rate is insufficient to produce a distal pressure greater than 32 mm. Hg. That the techniques used were at least qualitatively accurate at these low pressure levels is demonstrated by a case in which one

renal artery was perfused during resection of a thoracoabdominal aneurysm. In this case, the calibrated renal perfusion rate closely approximated the measurable renal blood flow (Fig. 5).

Group 2, Cardiopulmonary By-pass.—In the case of cardiopulmonary by-pass, with the pump-oxygenator, this study again demonstrates that a flow rate of 35 c.c. per kilogram of body weight supports a pressure ranging from 35 to 60 mm. Hg. This represents a mean pressure of 51 per cent of the preoperative level. In spite of an almost fourfold increase in the calculated renal vascular resistance, renal blood flow was maintained at 24 per cent of control values (Fig. 6). Since a decrease in cerebral vascular resistance is the general rule during periods of moderate hypotension, the decrease in cerebral blood flow should be proportionately less than the fall in blood pressure.[10] It should be pointed out that this is in sharp contrast to renal blood flow which showed a proportionately greater reduction than blood pressure. The cerebral circulation has a second compensatory capacity through increased oxygen extraction.[10] Hence, as previously demonstrated, cerebral and renal circulation must remain sufficient to prevent ischemic damage.[1] When separate perfusion circuits for the carotid arteries were necessary during excision of aneurysms located in the aortic arch, flow rates of 450 to 800 c.c. per minute have appeared to be adequate.

SUMMARY

1. Controlled extracorporeal circulation with a pump for aortic by-pass has been employed during the resectional therapy of aneurysms located in the descending thoracic aorta. Studies of blood pressure, renal blood flow, and glomerular filtration rate were performed during these procedures. These observations indicate that a pump flow rate of 20 c.c. per kilogram of body weight is necessary to support a lower aortic pressure sufficient to allow renal function.

2. Controlled extracorporeal circulation with a pump-oxygenator for cardiopulmonary by-pass has been employed during the resection and replacement of aneurysms located in the ascending and transverse aortic arch. Similar studies performed in these patients indicate that a perfusion rate of 35 c.c. per kilogram of body weight supports an aortic pressure sufficient to allow renal function.

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(For Discussion, see page 641)

PHYSIOLOGIC AND PHARMACOLOGIC STUDIES OF COLLATERAL PULMONARY FLOW

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INTRODUCTION

PATHOLOGIC studies have demonstrated the tremendous increase in number and size of bronchial vessels that may occur in certain types of cardiac and pulmonary diseases.[1-3] Physiologic studies of collateral pulmonary flow have been meager, primarily because of technical difficulties inherent in the methods devised to measure this flow. Techniques have been described in which measurements of blood flow have been made on isolated bronchial arteries,[4] single lobes,[5, 7] and in lung-thorax and lung-esophagus preparations.[5, 11] Indirect measurements of bronchial flow in dogs and human beings by means of gas analysis data have also been reported.[6] With the aid of effective pump-oxygenators, it has become feasible to study collateral pulmonary flow in the intact animal. We believe that to understand more fully the role of collateral pulmonary flow in pathologic states, more information regarding this circulation under normal conditions would be most desirable.

METHODS

The acute experiments described here were performed on 25 mongrel dogs, 8 to 30 Kg. in weight. They were anesthesized with pentobarbital sodium, 5 mg. per kilogram and given heparin, 2 mg. per kilogram, intravenously. Pressures in the femoral artery and in a branch of the pulmonary artery were registered with plastic cannulae connected to strain gauges, amplifiers, and a multichannel direct writing oscillograph. Pressure in the inferior vena cava was read directly in a plastic tube inserted via a femoral vein. The heart and great vessels were exposed under positive pressure endotracheal respiration by a bilateral transsternal thoracotomy through both fourth intercostal spaces. Plastic cannulae for the withdrawal of venous blood were inserted into the right ventricle through the right auricular appendage and into the superior vena cava through a jugular vein. The pulmonary artery was then ligated at its base and, thus, all venous blood from the right heart was diverted through a heart-lung machine described elsewhere[8] whence it was returned to the systemic circulation through a femoral or carotid artery. The left ventricle was cannulated at the apex and all blood from it drained into a graduated reservoir which was placed 10 cm. below the dog's spine. Blood from

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this reservoir was re-injected by a variable speed Sigmamotor pump into the pulmonary artery through a cannula distal to the ligature. With this arrangement, the volume of blood which comes from the pulmonary veins into the left heart and into the reservoir must be the sum of the volume pumped from the reservoir into the pulmonary artery plus the volume of the collateral circulation to the lungs. When a steady state obtains in this system the volume of blood injected into the pulmonary artery per minute is known and constant; when the

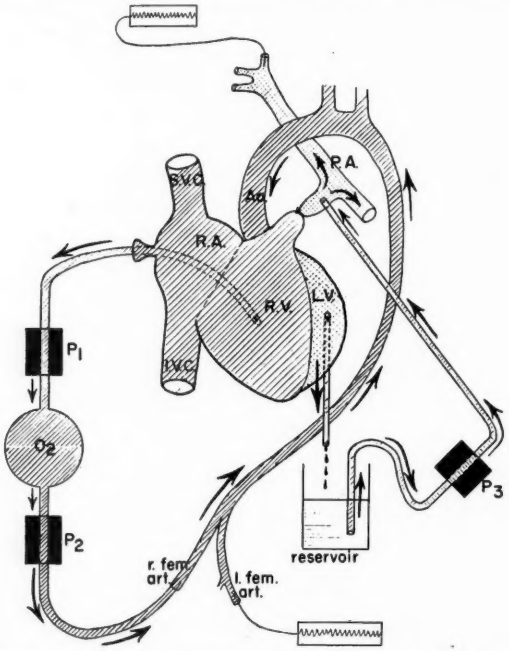

Fig. 1.—Diagram of separate perfusion of greater and lesser circulations. Strain gauges connected to branch of right pulmonary artery and left femoral artery. *R.V.*—Right ventricle. *R.A.*—Right atrium. *S.V.C.*—Superior vena cava. *I.V.C.*—Inferior vena cava. P_1—Pump which aspirates venous blood from right ventricle. O_2—Gas exchange unit ("artificial lung"). P_2—Pump which injects arterialized blood into systemic artery. A_o—Aorta (occluding clamp not shown). *P.A.*—Pulmonary artery. *L.V.*—Left ventricle. P_3—Pump which injects blood from the reservoir into pulmonary artery.

blood (collected from the left ventricle) exceeds the flow to the pulmonary artery the difference must be due to collateral circulation (Fig. 1). The quantity of this collateral flow per standard observation period can thus be read directly from the blood level in the reservoir. In some experiments a recording pH meter measured and registered the pH of the blood going from the machine to the animal or from the reservoir to the lung.

The systemic circulation of the animals was perfused with arterial flows ranging from 25 c.c. per kilogram per minute to 70 c.c. per kilogram per minute. This resulted in systemic arterial pressures ranging from 40 to 110 mm. Hg, systolic. Pressures in excess of this were observed after administration of pressor agents such as phenylephrine hydrochloride (Neosynephrine) or Arterenol.

By placing a clamp across the aorta, errors, due to blood entering the left ventricle through the aortic valve or via the coronary circulation, were avoided. The heart after a variable time became cyanotic, dilated and went into arrest. Observations were made only when a steady state existed and the following conditions obtained: (a) the animal had intact reflexes and excellent jaw tone, (b) sufficient time elapsed so as not to overlook any change which occurred gradually and, (c) readings were taken during identical phases of the respiratory cycle. All data reported here were taken from significant observations, when the above precautions were observed, and when at least 4 measurements during successive one-minute periods indicated a steady state.

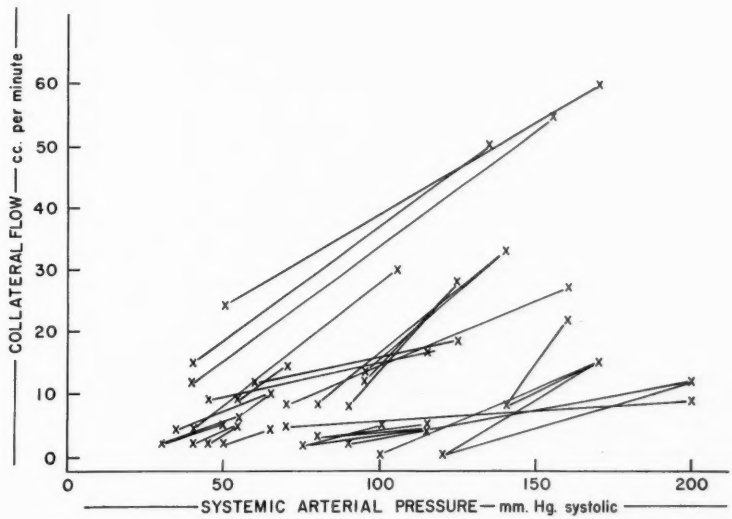

Fig. 2.—Effect of variations of systemic arterial pressure upon collateral flow. Points belonging to one observation are connected by solid lines. Changes in systemic pressure effected by variation of arterial flow rate or by pressor agents.

TABLE I. EFFECT OF VARIATION OF SYSTEMIC ARTERIAL PRESSURE ON COLLATERAL FLOW

DOG NO.	WEIGHT (KG.)	F.A.P.* (MM. Hg SYSTOLIC) FROM	TO	RISE OR FALL EFFECTED BY	COLLATERAL FLOW (ML./MIN.) FROM	TO
259	10	100	75	Flow through pump	5	2
259	10	75	115	Flow through pump	2	4
259	10	115	80	Flow through pump	4	3
259	10	80	115	Flow through pump	3	5
266	24	70	160	Neosynephrine	8	27
266	24	160	140	After Neosynephrine	22	8
266	24	140	170	Neosynephrine	8	15
275	30	80	140	Epinephrine	8	33
275	30	140	95	After epinephrine	33	13
275	30	90	125	Arterenol	8	28
275	30	125	95	After Arterenol	28	12

*F.A.P. = Femoral artery pressure.

RESULTS

1. *Systemic Artery Pressure and Collateral Blood Flow.*—In 25 dogs, a direct relationship between mean systemic arterial pressure and collateral flow was observed (Fig. 2, Table I). This occurred whether the increases in pressure

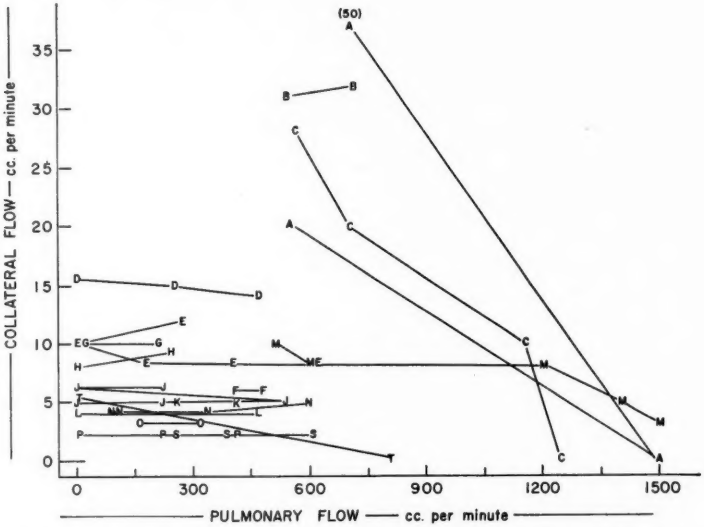

Fig. 3.—Effect of pulmonary artery flow on collateral flow. Points belonging to one observation (systemic arterial pressure constant during the observation period) are connected with a solid line. Each letter pertains to one experiment.

TABLE II. EFFECT OF PULMONARY ARTERY FLOW ON COLLATERAL FLOW

DOG NO.	WEIGHT (KG.)	PULMONARY FLOW (ML./MIN.) FROM	PULMONARY FLOW (ML./MIN.) TO	COLLATERAL FLOW (ML./MIN.) FROM	COLLATERAL FLOW (ML./MIN.) TO	F.A.P.* (MM. Hg SYSTOLIC) FROM	F.A.P.* (MM. Hg SYSTOLIC) TO
259	10	325	100	4	4	95	95
259	10	100	590	4	5	95	100
259	10	590	88	5	4	100	100
264	20	0	220	5	5	55	55
264	20	220	530	5	5	55	55
264	20	530	0	5	6	55	55
264	20	0	220	6	6	55	55
264	20	220	400	2	2	30	30
264	20	400	0	2	2	30	30
264	20	0	210	10	10	65	65
275	30	1,200	500	8	10	80	80
275	30	500	1,500	8	3	80	80
275	30	1,500	600	3	8	80	80
275	30	600	1,400	8	5	80	80

*F.A.P. = Femoral artery pressure.

were occasioned by pressor agents, or increases in blood flow. In several experiments, systemic flow was increased but blood pressure was kept constant by means of hexamethonium. Increases in collateral flow did not occur. At systolic

pressures of 90 to 120 mm. Hg, collateral blood flow was in the range of 0.5 to 1.0 per cent of total systemic blood flow when flow in the pulmonary circuit equalled systemic perfusion volume.

2. *Pulmonary Artery Perfusion and Collateral Blood Flow.*—No consistent changes in collateral blood flow were noted when pulmonary perfusion rates varied between 0 and 30 per cent of the total systemic flow. At this rate, collateral flow equalled 2 to 3 per cent of the total systemic flow. At pulmonary flows in excess of 30 per cent of systemic flow, an inverse relationship between pulmonary arterial flow and collateral flow was seen (Fig. 3, Table II).

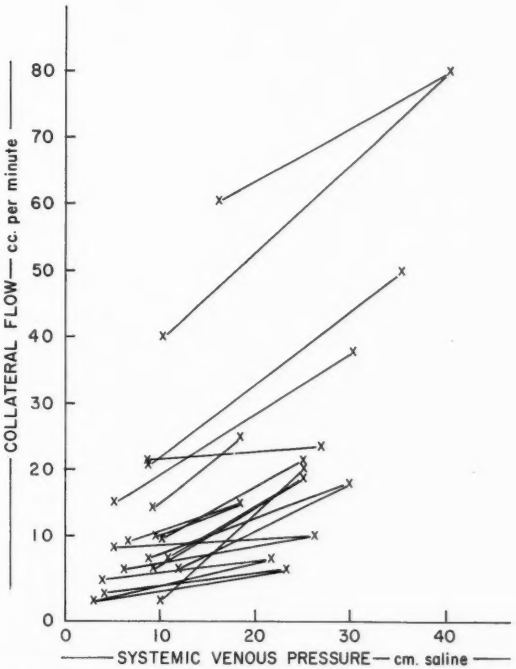

Fig. 4.—Effect of variation of systemic venous pressure upon collateral flow. Points belonging to one observation are connected by solid lines.

In several experiments, collateral flow was determined without pulmonary circuit perfusion. Blood was collected for measurement by cannulae in the pulmonary artery and left ventricle. Blood collected from the pulmonary artery thus constituted retrograde collateral flow. The partition of collateral flow between pulmonary artery and pulmonary veins was variable and a consistent pattern was not observed. The study of collateral flow partition, however, needs further investigation.

3. *Venous Pressure and Collateral Flow.*—In 8 dogs, increases of venous pressure resulted in increases of collateral flow in 11 of 14 experiments. This

TABLE III. EFFECT OF VARIATION OF SYSTEMIC VENOUS PRESSURE ON COLLATERAL FLOW

DOG NO.	WEIGHT (KG.)	V.P.* (CM. SALINE) FROM	V.P.* (CM. SALINE) TO	COLLATERAL FLOW (ML./MIN.) FROM	COLLATERAL FLOW (ML./MIN.) TO	F.A.P.† (MM. Hg SYSTOLIC) FROM	F.A.P.† (MM. Hg SYSTOLIC) TO
268	24	11	25	7	19	75	75
268	24	25	9	19	5	75	60
268	24	12	30	5	18	60	60
268	24	30	8	18	7	60	60
268	24	9	18	10	15	55	45
268	24	18	7	15	9	45	40
269	16	4	22	3	7	70	70
269	16	22	3	7	0	70	75
269	16	4	23	1	5	75	75
269	16	23	3	5	0	75	75
272	14	9	18	12	25	55	90
272	14	16	40	60	80	170	135
272	14	40	10	80	40	135	100

*V.P. = Venous pressure.
†F.A.P. = Femoral artery pressure.

increase ranged up to 400 per cent of control values. Decreases in venous pressure (by decreasing blood volume) were followed by reductions in collateral flow (Fig. 4, Table III).

4. *Pulmonary Ventilation and Collateral Flow.*—In 6 of 10 significant observations (see Table I), collapse of the lungs and arrest of positive pressure respiration caused a decrease of collateral blood flow to the lungs up to 40 per cent of the control value. When positive pressure respiration was resumed after its arrest the collateral blood flow increased in 5 of 9 observations. There was no significant variation of the arterial pressure during these observations.

TABLE IV. EFFECT OF PULMONARY VENTILATION ON COLLATERAL FLOW

DOG NO.	WEIGHT (KG.)	RESPIRATION	COLLATERAL FLOW (ML./MIN.) FROM	COLLATERAL FLOW (ML./MIN.) TO	F.A.P. (MM. Hg SYSTOLIC) FROM	F.A.P. (MM. Hg SYSTOLIC) TO
227	30	Off	9	7	170	200
227	30	On	7	12	200	200
227	30	Off	12	7	200	200
227	30	On	7	7	200	200
227	30	On	22	25	100	100
231	?	Off	8	9	140	170
231	?	On	9	11	140	170
231	?	Off	11	7	140	170
231	?	On	7	13	150	150

5. *Ventilation of Lungs With 10 Per Cent CO_2 and Oxygen.*—On ventilating the lungs with 10 per cent carbon dioxide and 90 per cent oxygen, a rapid fall in pulmonary blood pH was noted without changes in systemic blood pH or pressure. In 9 of 11 experiments, increases of collateral flow up to 160 per cent above control values were observed (see Table I). When ventilation with 100 per cent oxygen was resumed, collateral flow decreased in 8 of 11 significant observations. When the separately perfused lungs were ventilated with pure oxygen but the heart-lung machine supplied with 10 per cent carbon dioxide in 90 per cent oxygen, no significant changes in collateral blood flow to the lungs were observed.

TABLE VA. EFFECT OF INHALATION OF 10 PER CENT CO_2-90 PER CENT O_2 MIXTURE ON COLLATERAL FLOW

DOG NO.	WEIGHT (KG.)	INHALATION OF	pH OF PULMONARY BLOOD FROM	pH OF PULMONARY BLOOD TO	COLLATERAL FLOW (ML./MIN.) FROM	COLLATERAL FLOW (ML./MIN.) TO	F.A.P. (MM. Hg SYSTOLIC) FROM	F.A.P. (MM. Hg SYSTOLIC) TO
263	20	10% CO_2–90% O_2	7.18	7.00	45	75	45	45
263	20	100% O_2	7.05	7.23	40	7	55	40
265	16	10% CO_2–90% O_2	7.85	7.07	5	8	55	55
265	16	100% O_2	7.07	7.88	8	3	55	65
266	24	10% CO_2–90% O_2	7.75	7.18	6	10	70	70

TABLE VB. EFFECT OF SYSTEMIC HYPERCAPNIA AND ACIDEMIA ON COLLATERAL FLOW

DOG NO.	WEIGHT (KG.)	GAS TO MACHINE	pH OF SYSTEMIC BLOOD FROM	pH OF SYSTEMIC BLOOD TO	COLLATERAL FLOW (ML./MIN.) FROM	COLLATERAL FLOW (ML./MIN.) TO	F.A.P. (MM. Hg) FROM	F.A.P. (MM. Hg) TO
273	30	10% CO_2–90% O_2	7.28	7.23	30	18	75	55

6. *Serotonin and Collateral Flow.*—In 4 experiments, 1 to 10 mg. of serotonin was injected into the pulmonary circuit while other factors were kept constant. Marked increases in pulmonary artery pressure occurred, but no significant changes in collateral flow appeared in 2 experiments while in 2 others, complete suppression of collateral flow resulted (Table VI, B). Serotonin injected into the systemic circulation on the other hand, caused a pronounced sustained rise in collateral flow in 7 out of 9 experiments. The increase persisted for periods as long as 60 minutes and then diminished gradually (Table VI, A). Repeated administration of serotonin resulted in further increases in collateral flow. The systemic arterial pressure dropped transitorily but the pulmonary artery pressure remained high in these experiments.

TABLE VI. EFFECT OF SEROTONIN

DOG NO.	WEIGHT (KG.)	SEROTONIN (MG.)	COLLATERAL FLOW (ML./MIN.) FROM	COLLATERAL FLOW (ML./MIN.) TO	P.A.P.* (MM. Hg) FROM	P.A.P.* (MM. Hg) TO	F.A.P. (MM. Hg SYSTOLIC) FROM	F.A.P. (MM. Hg SYSTOLIC) TO
A. Effect of Serotonin to Systemic Circulation on Collateral Flow								
227	30	10	15	23			200	160
228	23	10 plus 5 Neosynephrine	22	19			100	150
231	?	10	7	14			150	120
266	24	20	15	27	17	40	170	130
269	16	10	3	12	15	23	90	90
272	14	20	25	45	45	20	70	70
273	30	5	0	40	50	60	50	40
275	30	10 plus 30	0	0			50	50
276	30	10 plus 10	2,0	5,0	22	25	90	75
B. Effect of Serotonin to Pulmonary Circulation on Collateral Flow								
272	14	10	30	25	25	50	70	70
273	30	5	28	0	32	50	70	50
275	30	10	14,12	32,0,0,0	12	60	95	75
276	30	10	8, 6	12	27	55	60	50

*P.A.P. = Mean pulmonary artery pressure.

7. *Air Embolism and Collateral Flow.*—In 5 out of 6 experiments in 3 dogs, embolization of the pulmonary artery with air resulted in significant

TABLE VII. AIR EMBOLISM (PULMONARY ARTERY)

DOG NO.	WEIGHT (KG.)	AIR IN P.A. (C.C.)	COLLATERAL FLOW (ML./MIN.) FROM	COLLATERAL FLOW (ML./MIN.) TO	F.A.P. (MM. Hg SYSTOLIC) FROM	F.A.P. (MM. Hg SYSTOLIC) TO
271	?		25	56	125	110
272	14	10	30	37	70	70
272	14	10	35	42	70	70
272	14	20	34	35	70	70
273	30	10	10	25	50	50
273	30	10	10	15	50	50
275	30	(At end of experiment)	0	0		170

increases in collateral blood flow to the lungs when other factors were kept constant (Table VII). Air embolism was accompanied by marked prolonged increases in pulmonary artery pressure.

DISCUSSION

When the lesser circulation is perfused separately from the systemic circuit, any increase in the blood volume of the lesser circulation can come only from blood vessels which connect the 2 systems, i.e., the bronchial vessels. In addition to supplying the lung, however, the bronchial arteries also supply the mid-portion of the esophagus and about one third of the flow drains into the systemic venous system via the bronchial artery flow drain into the pulmonary capillary network and/or into the pulmonary veins.[9, 10] The term, "collateral pulmonary flow," was used deliberately in this report for our method measures only that part of bronchial artery flow which drains into the pulmonary veins. Our experiments indicate that, with "normal" blood pressures, 0.5 to 1 per cent of the total systemic arterial flow is carried into the lungs by way of collateral circulation. This figure is comparable to that obtained by previous workers.[4, 7, 11] The direct relationship between systemic arterial pressure and collateral blood flow is quite definite and consistent. The hemodynamic effect of increasing pressure within the bronchial arteries outweighs any contraction of the bronchial arteries which may result from the administration of pressor agents; increases of systemic arterial pressure (regardless of how produced) result in augmented collateral pulmonary flow.

Our data confirm previous studies which pointed to an inverse relationship between pulmonary artery flow and collateral flow to the lungs.[7, 11] In contrast, the relationship between pulmonary artery pressure and bronchial artery flow appears ill defined or nonexistent.

The augmentation of collateral pulmonary flow, following increases in systemic venous pressure, deserves further investigation. Elevated pressures in the systemic and azygos veins might cause a reversal of flow in the bronchial veins and thus drainage of systemic venous blood into the pulmonary venous channels. The elevation of venous pressure seen in cardiac decompensation might thus have an important effect on collateral pulmonary circuit.

The increases in collateral arterial flow following the ventilation of the lungs with 10 per cent carbon dioxide and oxygen are probably due to a local action of carbon dioxide within the lung itself. The addition of carbon dioxide to the systemic circulation was without effect. Other investigators have also shown that ventilation of the lungs with high carbon dioxide mixtures causes pulmonary vasomotion.[12, 13] Whether this carbon dioxide effect is due to changes in pH or the carbon dioxide molecule per se has not as yet been investigated.

The results of administration of serotonin were different depending upon its site of administration. When given into the pulmonary circuit, decreases or arrest of collateral flow occurred, whereas serotonin administration into the systemic circulation produced marked increases of bronchial flow to the lungs. The reason for this difference is not apparent. An explanation which we have considered is that the locally administered drug reaches the pulmonary vessels first, in sufficient concentration to cause severe prolonged contraction of the pulmonary vasculature and bronchial muscles, resulting in secondary constriction of the collateral vessels.

The increase in collateral blood flow which followed air embolism was extremely interesting. The elevated pulmonary artery pressure seen in air embolism was similar in degree to that observed after serotonin administration. The increase in collateral pulmonary flow after air embolism and the decrease following serotonin administration indicates that elevation of pulmonary artery pressure per se does not cause the observed changes, but mechanical obstruction of pulmonary blood flow after embolization is probably responsible for the increased collateral flow. The effect may be compared with the effect of reduced pulmonary artery perfusion. Increased bronchial flow has been suggested as the mechanism causing hemorrhagic pulmonary infarction following pulmonary embolization and this concept finds support from our data.

It is commonly believed that those factors which cause acute increases of flow in the blood vessels are also responsible for the dilatation of blood vessels seen when such factors are operative for long periods of time. Collateral pulmonary flow is markedly increased in certain congenital cardiac conditions, pulmonary infections, and obstruction of the pulmonary arteries. Whether the increased collateral blood flow to lungs in chronic disease is mediated by any of the factors shown to cause acute changes would seem to deserve further investigation.

SUMMARY

1. A method has been developed for measuring collateral circulation to the lungs by a technique utilizing independent perfusions of the systemic and pulmonary circulations.

2. With "normal" blood pressures, the anastomotic channels between bronchial arteries and pulmonary veins carry 0.5 to 1.0 per cent of the total arterial blood flow, per minute.

3. The collateral blood flow to the lungs is directly related to systemic arterial pressure.

4. Changes in pulmonary artery flow rate did not consistently influence collateral blood flow to the lungs at pulmonary flow rates below 30 c.c. per kilogram per minute. At higher pulmonary flow rates there was in inverse relationship between flow in the pulmonary artery and collateral flow.

5. Increases in systemic venous pressure resulted in parallel increases of the collateral blood flow to the lungs.

6. Deflation of the lungs can cause a decrease in bronchial arterial flow ranging up to 50 per cent of control values.

7. The use of 10 per cent carbon dioxide in oxygen to ventilate the lung (but not the pump-oxygenator) increases bronchial flow markedly over control values when 100 per cent oxygen is used.

8. Administration of serotonin (5-hydroxytryptamine) markedly increased collateral flow when the drug was injected into the systemic circuit but decreased collateral flow when injected into the pulmonary circuit.

9. Air embolism caused increased collateral blood flow to the lungs.

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(For Discussion, see page 641)

AN EXPERIMENTAL APPROACH TO CARDIOSPASM: APPRAISAL OF THE FINNEY PYLOROPLASTY IN THE PREVENTION OF ESOPHAGITIS FOLLOWING THE HELLER MYOTOMY

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THE problem of esophagitis complicating operations for benign diseases of the esophagogastric junction remains a major one in surgery. Ripley and associates[1] have reported a group of 65 patients treated with esophagogastrostomy or cardioplasty and, of these, 40 had evidence of esophagitis postoperatively. Barrett and Franklin[2] have also observed a distressingly high incidence of esophagitis following esophagogastrostomy. Of 25 patients subjected to esophagogastrostomy or cardioplasty for cardiospasm, they discovered only 5 patients completely free from evidence of esophagitis. More recently Hawthorne and his co-workers[3] have reported that 21 per cent of 35 patients with achalasia, treated by the Heller operation, developed dysphagia, bleeding, or retrosternal pain postoperatively. This has also been the experience of Alnor and Wanke in Germany[4] who found esophagoscopic and/or radiographic evidence of esophagitis in all of 17 patients with cardiospasm treated by esophagogastrostomy.

It is generally agreed that the most important etiologic factor contributing to a poor surgical result is the reflux of acid-peptic juice into the esophagus, secondary to alteration of the esophagogastric sphincter mechanism by operation. This opinion is borne out experimentally by experience with dogs in the laboratory. In a study of esophagitis in dogs, following upper gastrectomy of varying degree, Hoag, Kiriluk, and Merendino[5] demonstrated that if the esophagogastric junction was not removed esophagitis was rare, but if the junction was resected with the proximal stomach esophagitis was a universal finding. Geever and Merendino[6] evaluated esophagitis in dogs subjected to the Grondahl operation and to Heller myotomy and found that when gastric secretion was stimulated by intramuscular injections of histamine in beeswax-oil, both of these operations were attended by esophagitis. The severity of the inflammatory reaction was augmented by vagotomy. Although vagotomy reduces the cephalic phase of gastric secretion, it also produces gastric atony, delays gastric emptying, and thereby excites the antral phase of gastric secretion. In the presence of an

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incompetent sphincter mechanism at the esophagogastric junction with an intact pyloric sphincter, greater reflux into the esophagus is produced and probably accounts for the more severe reaction following vagotomy.

Girvin and Merendino[7] have observed that, following histamine stimulation, dogs previously subjected to a Heller procedure combined with vagotomy and Finney pyloroplasty, the incidence and severity of esophagitis is markedly reduced. As an ancillary gastric drainage procedure, Finney pyloroplasty also minimizes esophagitis in dogs following esophagogastrostomy.[8] It would seem that if reflux of gastric juice into the esophagus is an important factor in the production of esophagitis any procedure which speeds gastric emptying should not only reduce reflux but also reduce the antral phase of gastric secretion. In this manner, it would appear that one may minimize or prevent esophagitis as a complication of operations on the cardiac sphincter.

The purpose of this study was to evaluate the efficacy of Finney pyloroplasty following the Heller myotomy in preventing esophagitis in histamine stimulated dogs.

Method.—Two groups of dogs were studied. The first group consisted of 12 dogs weighing from 10 Kg. to 20.5 Kg., with an average weight of 14.5 Kg. These animals were subjected to a Heller myotomy only. This averaged 8 cm. in length. The second group of dogs consisted of 12 animals weighing from 11 Kg. to 26 Kg., with an average weight of 17.6 Kg. These dogs were subjected to a Heller myotomy averaging 8.3 cm. in length and, in addition, a Finney pyloroplasty with an average stoma size of 5.7 cm.

OPERATIVE PROCEDURE

All of the animals were anesthetized with intravenous Nembutal (26 mg./Kg.) and endotracheal ether administered through a Palmer respirator. The abdomen was entered through a midline incision extending from the xyphoid process to the umbilicus and the terminal esophagus exposed by mobilizing the left lobe of the liver and dividing the left portion of the phreno-esophageal ligament.

The Heller myotomy was then performed, taking care to extend the myotomy from as high on the esophagus as possible to well onto the anterior surface of the stomach, avoiding the identifiable branches of the vagi. Hemostasis was obtained with ligatures of No. 3-0 cotton and the esophageal hiatus repaired with a continuous No. 3-0 cotton suture. In the experimental group of dogs, the Finney pyloroplasty was then done in the usual manner with a posterior layer of No. 3-0 cotton sutures, an inverting row of No. 3-0 chromic catgut on the mucosa and an anterior layer of No. 3-0 cotton sutures.

The abdominal incision was closed in layers and the chest placed on continuous water-seal drainage for approximately 2 hours. Water and liquid rations were allowed ad libitum for 2 days, then regular kennel rations were given. Penicillin, 200,000 units, and streptomycin, 1.0 Gm., were given intramuscularly daily for 5 days postoperatively.

OTHER STUDIES

At the end of a 30-day recuperative period, each dog was esophagoscoped to determine the incidence of spontaneous esophagitis in each group and shortly thereafter the intramuscular injections of histamine in beeswax-oil was begun. Histamine was given to each dog in doses of 30 mg. histamine-base per day for 45 days or until death, at which time autopsy was performed. Those dogs surviving the 45-day period of stimulation were sacrificed and appropriate photographs and specimens for histologic study were taken.

Five healthy dogs, upon which no operation had been performed, were given histamine concurrently to serve as controls on the potency of the histamine preparation being given the two other groups of dogs. These animals were autopsied and studied in the same manner as the others.

Fig. 1.

RESULTS

Four of the 5 unoperated animals died during the 45-day period of histamine stimulation and all of these had moderate to severe gastric and/or duodenal ulcers. The fifth dog survived the full period and when sacrificed showed no gastrointestinal ulceration. The incidence of gastrointestinal ulcers was, therefore, 80 per cent in these control dogs.

One of the Heller dogs did not survive to be stimulated with the histamine preparation. A few days after being esophagoscoped he died of an acute febrile

illness which proved to be distemper. The remaining 11 dogs received histamine injections as described.

Spontaneous esophagitis did not occur in those animals subjected to Heller myotomy only, but after the administration of histamine 8 of 11, or about 72 per cent, had gross or microscopic evidence of esophagitis (see Fig. 3). Fig. 1 is a

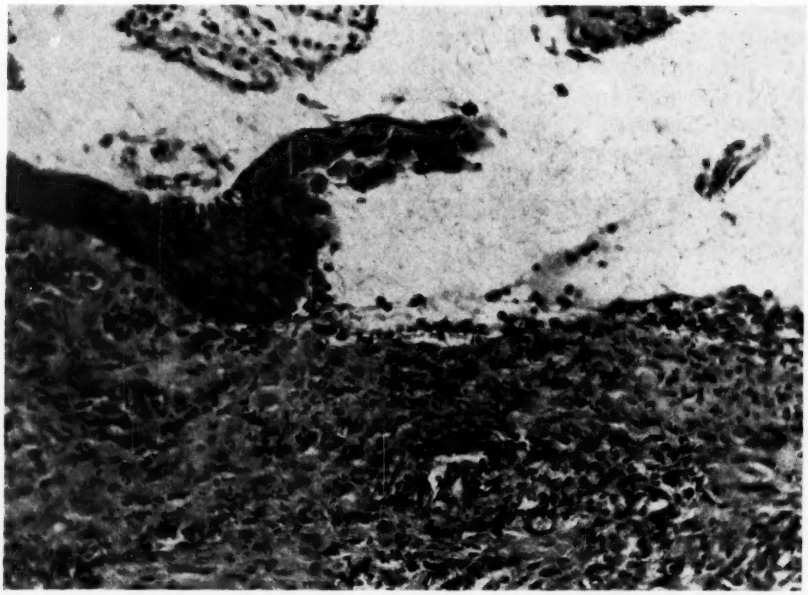

Fig. 2.

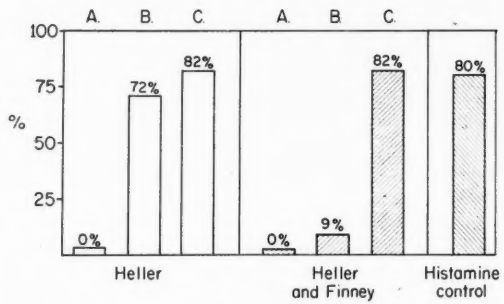

Fig. 3.—Column *A*—Spontaneous esophagitis. Column *B*—esophagitis after histamine stimulation. Column *C*—associated gastrointestinal ulcers.

representative specimen from one of the Heller dogs. The gastric ulcer is apparent. Grossly, the esophageal changes in this specimen consist of longitudinal areas of erythema and roughening of the mucosa. Microscopically, these areas show erosion of the mucosa and a submucosal inflammatory response. Fig. 2 is

a photomicrograph of such an area. Some of the Heller dogs had this minimal lesion, others had frank ulceration. Associated gastric or duodenal ulcers were found in 82 per cent of the group.

Fig. 4.

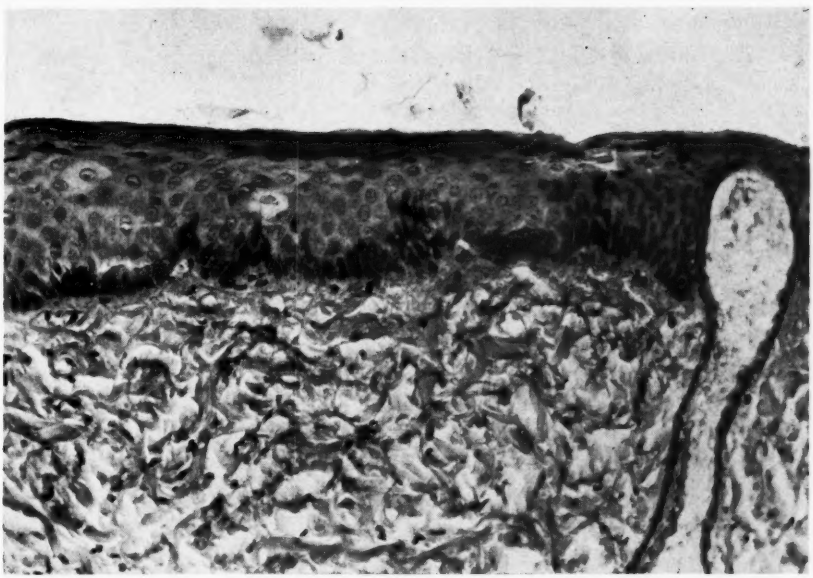

Fig. 5.

Spontaneous esophagitis was also not observed in the Heller-Finney group of animals. One of the original 12 dogs in this group expired from barbiturate overdosage at the time of esophagoscopy, but the remaining 11 were all given histamine injections in the manner outlined.

As illustrated in Fig. 3, only one of the Heller-Finney group of dogs had anything suggestive of esophagitis following the period of histamine stimulation in spite of the fact that 9 of the 11, or about 82 per cent, had associated gastric or duodenal ulcers. The one dog which was classified as having esophagitis died during a holiday and was not discovered for several hours. Marked autolytic changes precluded accurate gross or microscopic evaluation, but because esophagitis could not be disproved it was decided to include this dog in that group. Fig. 4 represents a typical specimen from an animal with the combined Heller-Finney procedure. The arrow indicates a gastric ulcer. The esophageal mucosa is entirely normal to gross inspection and microscopic study confirms this. Fig. 5 is a photomicrograph of this esophagus near the cardiac sphincter.

CONCLUSIONS

From the data derived from these experiments the following conclusions can be drawn:

1. Histamine in beeswax-oil is a potent ulcerogenic stimulus in dogs.

2. Esophagitis occurred in about 72 per cent of dogs stimulated with histamine following the Heller myotomy only.

3. In a similar group of animals with combined Heller myotomy and Finney pyloroplasty, the incidence of esophagitis was 9 per cent.

4. Finney pyloroplasty markedly reduces the incidence of esophagitis under the conditions of these experiments.

5. The addition of Finney pyloroplasty to the Heller operation appears to have merit, experimentally.

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(For Discussion, see page 641)

ESOPHAGEAL MOTILITY IN ACHALASIA (CARDIOSPASM) AFTER TREATMENT

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FOR several years, studies have been made in Mayo Clinic laboratory of esophageal motility in healthy persons and in persons having various disease states.[1-6] Pressures within the esophagus and at both the superior and inferior sphincters have been recorded in persons at rest and after deglutition.[4, 5] A great deal of information concerning the nature of the condition known as "cardiospasm" or "achalasia" has been obtained by physiologic methods (Fig. 1). In the present paper, it is our purpose to discuss the effect of treatment on esophageal pressure within the esophagus and at the inferior esophageal sphincter.

In the healthy person, the inferior esophageal sphincter opens in response to a well-coordinated swallowing act; in fact, a period of inhibition can be demonstrated at the cardia as the zone of elevated pressure in this region is temporarily abolished.[5] In achalasia, however, such a decrease in pressure rarely occurs. The final increase in pressure, which represents the termination of the deglutition reflex, occurs somewhat earlier in the patient having achalasia than in the normal person. These observations were made in patients who had not had effective treatment for cardiospasm.[7]

Therapy which completely restores normal esophageal motility to the patient with achalasia has not been achieved. Inasmuch as the condition is primarily a defect of esophageal peristalsis, treatment should logically be directed toward the restoration of the neuromuscular mechanism within the wall of the esophagus. Since such physiologic therapy is not yet available, present treatment must be directed toward decreasing the resistance at the lower esophageal sphincter. In so doing, care must be taken not to produce complete incompetence of the cardiac sphincter with resultant esophageal reflux. In our experience, satisfactory relief of dysphagia in cardiospasm usually can be obtained either by forceful dilatation of the inferior esophageal sphincter with the hydrostatic dilator or by means of a properly performed esophagomyotomy of the Heller type.[8] Inasmuch as we already have demonstrated that the resting pressures at the inferior esophageal

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sphincters of these patients are similar to those seen in the normal person,[7] we considered that measurement of the pressures at the cardia and terminal portion of the esophagus following either hydrostatic dilatation or esophagomyotomy would be of interest. We also wished to determine whether the relief of obstruction at the lower end of the esophagus would have any effect on the motility of the esophageal musculature.

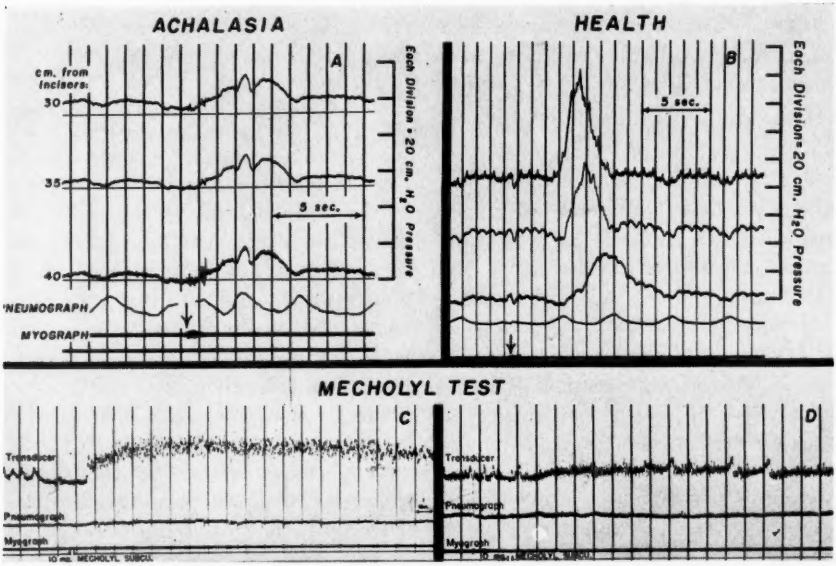

Fig. 1.—Esophageal pressures illustrating the essential differences between achalasia and health. *A*, Recording from lower half of esophagus of patient with achalasia, showing absence of peristaltic wave on swallowing. *B*, Normal peristaltic wave recorded from healthy person. *C*, Increase in pressure after subcutaneous injection of 10 mg. of Mecholyl in patient with achalasia. *D*, Absence of increase of pressure after injection of 10 mg. of Mecholyl in healthy person. (*From* Olsen, A. M., Ellis, F. H., Jr., and Creamer, B.: Cardiospasm [Achalasia of the Cardia], Am. J. Surg. 93: 299-307, 1957.)

METHODS AND PROCEDURES

Equipment.—Measurements of intraluminal pressures have been made directly by means of a miniature electromagnetic pressure transducer passed into the esophagus or indirectly by conduction of the pressures from multiple sites through open-tipped tubes connected to transducers placed externally to the body. After suitable amplification, the pressure changes were recorded photokymographically. Detailed information concerning the equipment employed for these measurements has been published previously.[1-6, 9] The instant of swallowing was recorded by skin electrodes attached to detect the action potentials of the accessory muscles of deglutition. Respiration was recorded by means of a tubular pneumograph belt attached to a glass spoon manometer.[9]

Technique.—The routine procedure for each test was to pass the transducer or open-tipped tubes through the mouth into the stomach. Then with the patient

Fig. 2.—Roentgenograms of the esophagus in a patient with achalasia. *a*, 1947, before hydrostatic dilatation. *b*, 1951, curling or tertiary contractions. No dysphagia. *c*, 1954, recurrent cardiospasm with mild dysphagia, before second hydrostatic dilatation. *d*, 1956, curling or corkscrew esophagus. No dysphagia.

in the supine position the resting pressures at the gastroesophageal junction were obtained by withdrawing one or more of the pressure detecting units from the stomach into the esophagus at 0.5 cm. intervals and recording the pressures at each site for 15 to 30 seconds. The patients were asked to refrain from swallowing during the recording of pressures. The process was then repeated with the patient swallowing after each withdrawal of the tubes.

The analysis of the pressures has been described previously.[5] On each tracing the position of the pressure pick-up unit at which the pressure deflections changed from a positive to a negative direction with inspiration was identified. This site was taken to be at or very near the level of the diaphragmatic hiatus. It was used as a reference point from which the distance of the recording sites above and below it were measured. The mean fundic pressure for each patient

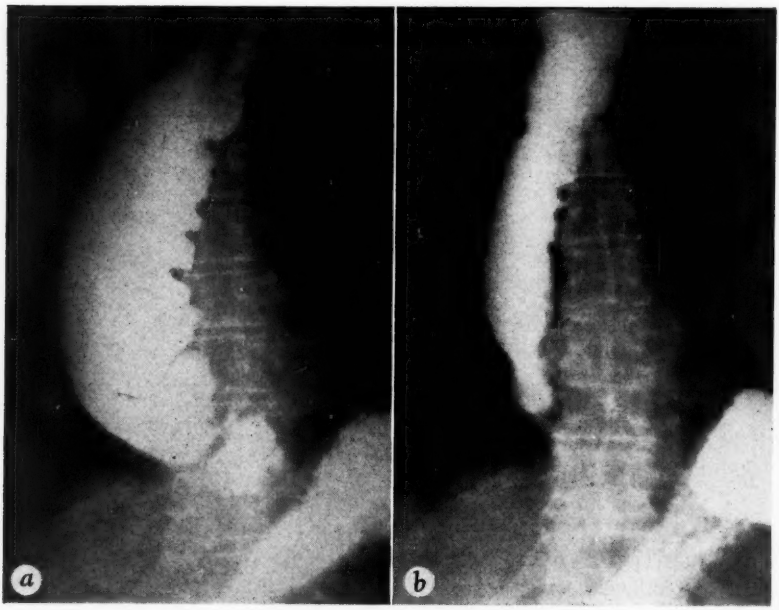

Fig. 3.—Roentgenograms of the esophagus in a patient with achalasia. *a*, Before surgery. *b*, After esophagomyotomy.

was designated as zero, and the resting pressures at the gastroesophageal sphincter and terminal esophagus were expressed in centimeters of water above or below this level. All pressures were measured at the end of expiration and of inspiration in the breathing cycle, as determined by the pneumographic tracing.

Patients Studied.—Control series: A study was made of 20 patients with achalasia—11 women and 9 men who had not had hydrostatic dilatation or esophagomyotomy. The mean age for this group was 46.9 years, with a range from 23 to 60 years.

Hydrostatic series: Seventeen patients were studied after hydrostatic dilatation. This group included 9 males and 8 females ranging in age from 16 to 60 years, with a mean age of 40 years.

Esophagomyotomy series: Records have been obtained from 31 patients with achalasia in whom operations of the Heller type had been performed on the cardia. Data will be presented concerning 8 patients from whom we were able to obtain resting pressures at the gastroesophageal junction both before and after operation. Five of these 8 patients were men and 3 were women. Their ages varied from 22 to 55 years, with a mean age of 45 years.

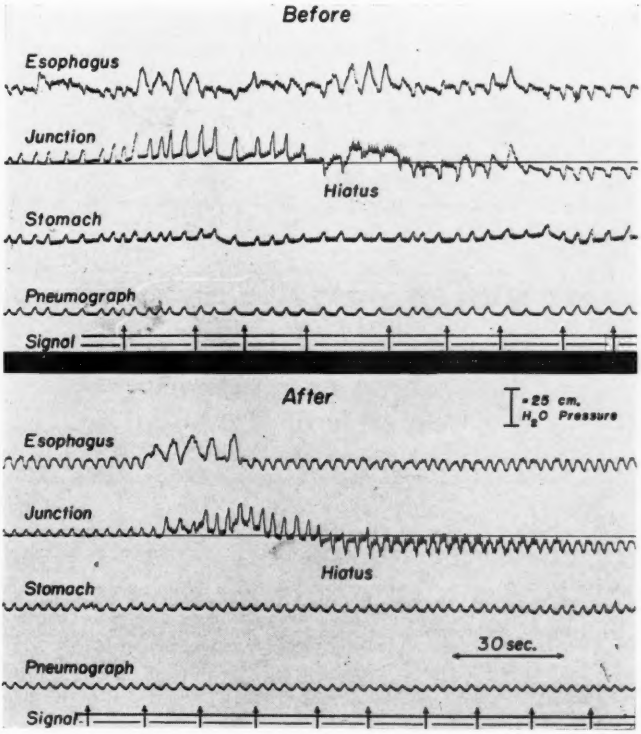

Fig. 4.—Record of resting pressures at esophagogastric junction as pressure unit is withdrawn from a patient's stomach into the lower portion of esophagus: before hydrostatic dilatation, showing zone of elevated pressure present above and below hiatus; after hydrostatic dilatation, showing that zone of elevated pressure persists below diaphragm but has been abolished above the hiatus.

RESULTS

After hydrostatic dilatation or esophagomyotomy, a diminution in the size of the esophagus frequently can be demonstrated roentgenographically. In fact, the esophagus often will present the appearance of diffuse spasm although the patient does not have obstruction on swallowing and does not have pain

(Figs. 2 and 3). Studies of intra-esophageal pressure did not reveal improvement in esophageal motility. Neither primary nor secondary peristaltic waves were seen and results of the Mecholyl test (Fig. 1, *c*) remained positive.[2] The corkscrew appearance of the esophagus after treatment is a phenomenon observed rather frequently by the roentgenologist,[10] and the roentgenographic silhouette is indistinguishable from clinically significant diffuse spasm.

However, the resting pressures at the esophagogastric junction are greatly altered by effective hydrostatic dilatation (Fig. 4), or esophagomyotomy (Fig. 5). Fig. 6 shows the mean resting pressure at the cardia of 17 patients treated

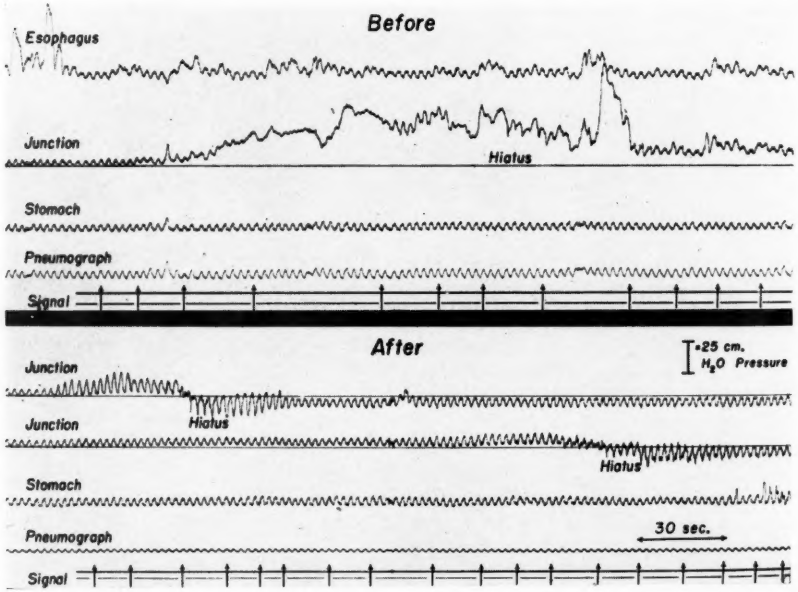

Fig. 5.—Record of resting pressures at esophagogastric junction on withdrawal of pressure unit from patient's stomach into the lower portion of the esophagus: before esophagomyotomy, zone of elevated pressure extending above and below esophageal hiatus; after esophagomyotomy, reduction in pressure and in width of zone of elevated pressure leaving only a segment of elevated pressure below the diaphragm.

with the hydrostatic dilator as compared with the resting pressures of 20 other untreated patients. A dramatic reduction in the resting pressures at both the end-expiratory and the end-inspiratory phases of breathing is apparent after dilatation (Fig. 6). The decrease in end-expiratory pressures is more apparent above the hiatus of the diaphragm than below it. The pressures at the end of inspiration are reduced, commencing 2.5 cm. below the hiatus and continuing upward into the terminal portion of the esophagus (Fig. 6). These differences in pressure prove to be significant when treated by statistical methods.

Actual pressure tracings illustrate the effect of the hydrostatic dilator (see Fig. 4). The pressure fluctuations with breathing and the reversal of these fluctuations are easily identified. The pressures below the point of respiratory

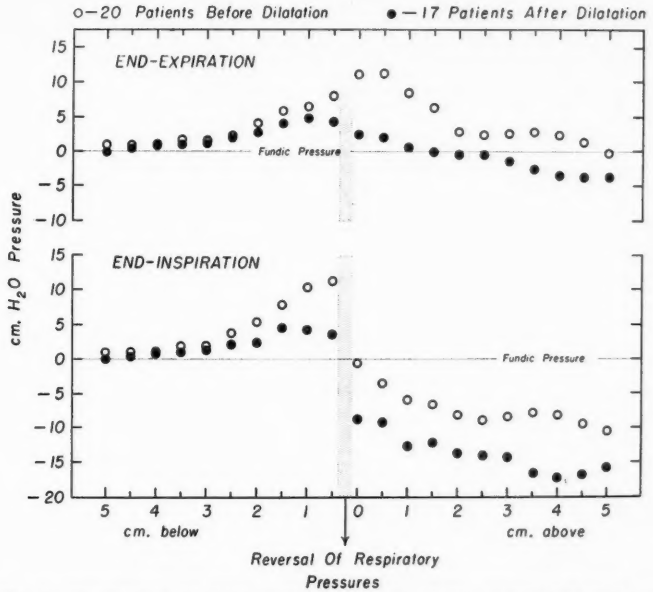

Fig. 6.—Comparison of mean resting pressures at the gastroesophageal sphincter at the end of expiration and the end of inspiration in 20 untreated patients with achalasia and 17 patients treated with the hydrostatic dilator.

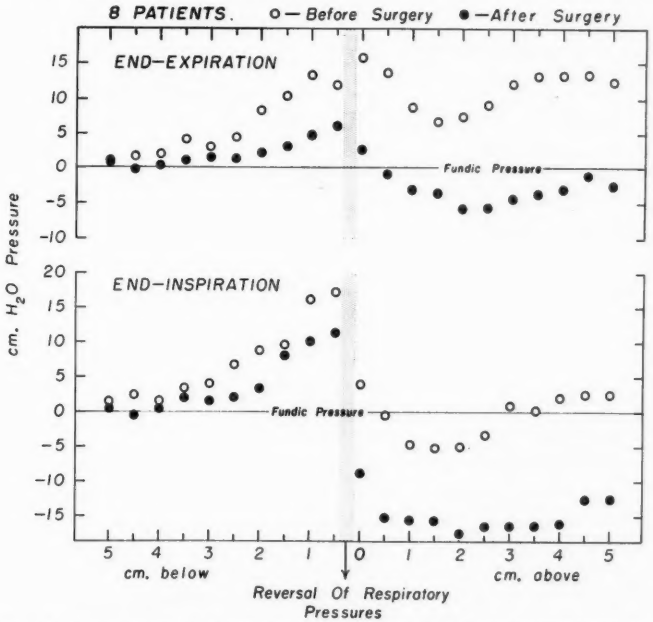

Fig. 7.—Comparison of mean resting pressures at the gastroesophageal sphincter at the end of expiration and the end of inspiration in 8 patients having achalasia prior to operation and the same 8 patients after esophagomyotomy.

reversal are nearly identical in records made before and after dilatation, but the area of elevated pressure above this point is reduced following hydrostatic dilatation.

The pressure tracings before and after esophagomyotomy are illustrated in Fig. 5. To be noted are the reduction in the width of the sphincteric zone and the complete elimination of the suprahiatal portion of the sphincter.

The mean resting pressures at the gastroesophageal junction obtained from all 8 patients before and after esophagomyotomy are plotted in Fig. 7. The values obtained before operation are high, commencing about 2 cm. below the point of respiratory reversal (hiatus) and continuing into the esophagus. After operation, the zone of elevated pressure at the end-expiratory phase of breathing is, for all practical purposes, abolished. The pressures at the end of inspiration are eliminated above the diaphragm, but the subhiatal portion of the sphincter remains. Pressures within the esophagus, in most patients with achalasia, are well above those detected in the fundus of the stomach. After operation, the esophageal pressures tend to return to more normal relationship, that is, below fundic pressure.

From these data we can conclude that either successful hydrostatic dilatation of the sphincteric zone or esophagomyotomy of the Heller type abolishes the supradiaphragmatic zone of elevated pressures found at the gastroesophageal sphincter in achalasia. It is our opinion that the remnant of the sphincter that remains just below the point of reversal of respiratory pressures is important in the prevention of reflux. Although this zone does not relax with swallowing in patients with achalasia, it is feeble enough to be overcome by the pressure build-up within the esophagus following deglutition.

COMMENT

Operative procedures which destroy the sphincteric property of the cardia permit regurgitation of gastric secretions, and the late results are almost invariably unsatisfactory.[11, 12] Thus, the Heyrovsky, Gröndahl and Wendel operations have been abandoned. Reflux esophagitis, although rare, may occur after hydrostatic dilatation. It has been our impression that regurgitant esophagitis develops infrequently after esophagomyotomy of the Heller type.[8] Apparently the secret of success is to disturb the anatomic relationships at the cardia as little as possible.[13]

At the time of this study, it is our opinion that both hydrostatic dilatation and cardiomyotomy are effective but not ideal methods of treating cardiospasm.[8] Neither procedure restores peristalsis in the esophagus. Both, however, are successful in reducing the resistance which must be overcome at the lower end of the esophagus without completely destroying the sphincteric mechanism. Present evidence suggests that the subhiatal portion of the sphincter should be preserved, as the integrity of this segment is important in the prevention of reflux.

SUMMARY

Findings of this study indicate that with rare exceptions the motility of the esophagus of patients with achalasia is not restored by any therapeutic procedure available at present. However, the suprahiatal portion of the zone of

high pressure at the inferior esophageal sphincter is usually abolished by either hydrostatic dilatation or esophagomyotomy and this reduces the resistance of the sphincter sufficiently to allow a more normal passage of esophageal contents into the stomach. Retention of the inferior hiatal portion of the sphincter apparently prevents reflux in these patients.

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(For Discussion, see page 641)

POSTOPERATIVE SODIUM EXCRETION FOLLOWING ADMINISTRATION OF HYPERTONIC SODIUM CHLORIDE SOLUTION

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THE observation of decreased urinary excretion of sodium postoperatively, usually accompanied by a decrease in concentration of serum sodium and in urinary volume, is well documented.[3, 4, 6, 10, 11, 12, 15] Numerous studies have been reported which attempt to elucidate the physiologic processes involved in this phenomenon. Hormonal influence, particularly aldosterone, translocation of the sodium ion to the intracellular and/or extracellular (interstitial) space, and altered renal tubular function have all been implicated.[1, 2, 5, 8, 9, 14, 16, 20]

Because of the multiplicity of factors concerned, a precise explanation of postoperative renal sodium retention has yet to be advanced. However, regardless of the exact mechanisms involved, it has been generally agreed that the ability of the normal kidney to excrete sodium is impaired early postoperatively. Since the work of Coller and his associates[3] in 1944, the restriction of sodium intake during this period has become routine.

Because this postoperative sodium retention occurs concomitantly with a decrease in the level of serum sodium, it was felt that the renal sodium retention might be a reflection of a need to conserve sodium early postoperatively in an effort to return the serum sodium toward a normal concentration. Considerable interest was aroused by the work of Winfield, Fox, and Mersheimer,[18] who, in 1951, using their "Balanced Electrolyte Solution," showed that the normal postoperative kidney does not obligatorily restrict sodium excretion. Zimmerman and Wangensteen,[19] in 1952, observed that restoration of serum sodium and chloride concentrations by the use of hypertonic sodium chloride solution frequently resulted in diuresis. In 1954, Hardy, Lovelace, and Wilson[8] reported on the clinical use of hypertonic saline postoperatively. Schlegel,[15] in 1954, considered the relation of postoperative serum sodium levels to urinary excretion, and suggested administering a sodium load, with sodium in excess of water, and measuring excretion.

In order to test this hypothesis, we decided to administer hypertonic sodium chloride solution postoperatively in an attempt to maintain normal serum sodium, and to measure urinary sodium excretion.

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METHODS

Thoracic surgical patients were chosen for this study because of minimal alteration of gastrointestinal tract function with only short-term dependence on parenteral feeding postoperatively. With regard to sodium metabolism, the response of thoracic surgical patients to surgical trauma is similar to that of patients undergoing other surgical procedures of comparable magnitude.[1, 7]

Five patients were given hypertonic sodium chloride solution intravenously and 5 patients received "routine" management, i.e., sodium restriction, during the postoperative period. All patients received approximately 2,000 c.c. of fluid intravenously on the day of operation, in addition to blood replacement. In the "Control" or routine management group, fluids consisted of 5 per cent dextrose in distilled water. The patients in the "Hypertonic Saline" group received 300 c.c. of 3 per cent sodium chloride solution as part of their 2 L. parenteral intake. In addition, these patients received 200 c.c. of 3 per cent sodium chloride solution on the first and second postoperative days. No other parenteral fluids were administered after the day of operation as all patients were able to ingest adequate amounts of oral fluids. A general ward diet was started on the first postoperative day. Oral intake during the first 3 postoperative days averaged approximately 2,000 c.c.

Electrolyte determinations were carried out preoperatively and daily during the first 5 postoperative days, using a Beckman DU Flame photometer for the sodium and potassium, the method of Schales for the chloride, and the method of Van Slyke for the carbon dioxide combining power. Preservative used in the 24-hour urine collection bottles consisted of 5 c.c. glacial acetic acid and two drops of toluene.

TABLE I

PATIENT	AGE	OPERATIVE PROCEDURE	PATHOLOGY
		"Control" Group	
W. W.	22	Left basals and lingula	Bronchiectasis
H. R. S.	33	Wedge biopsy, right upper lobe	Eosinophilic granuloma
S. K.	64	Left lower lobectomy	Hamartoma
J. R.	45	Right upper and right middle lobectomy and decortication	Bronchiectasis and empyema
C. N.	36	Dorsal segment left lower lobe and decortication	Bronchiectasis and empyema
		"Hypertonic Saline" Group	
H. S.	23	Left basal segments	Bronchiectasis
W. K.	60	Wedge resection, right lower lobe	Granuloma
O. M.	57	Left upper lobectomy	Carcinoma
L. S.	58	Right upper lobectomy	Cyst
C. M.	27	Excision of blebs and pleural symphysis	Pneumothorax

TABLE II

	MEQ./L.	PRE-OP.	OPER.	P.O. 1	P.O. 2	P.O. 3	P.O. 4	P.O. 5
				"Control" Group				
W. W.	*Serum*							
	Na	140	138	135	130	134	137	138
	Cl	103	105	99	98	97	97	—
	K	4.8	4.9	4.9	5.0	5.0	4.9	4.6
	CO_2	24	23	29	23	29	—	—
	Urine							
	Na	51	86	8	4	4	6	12
	Cl	50	93	4	49	26	15	33
	K	23	31	53	60	29	18	16
	Vol. (c.c.)	1,236	700	2,255	795	1,780	3,400	2,650
H. R. S.	*Serum*							
	Na	143	141	143	135	—	136	139
	Cl	106	103	100	92	94	96	100
	K	4.6	4.5	4.2	4.8	—	4.2	4.0
	CO_2	25	23	29	26	26	28	23
	Urine							
	Na	55	76	14	2	6	28	35
	Cl	67	112	36	20	20	19	27
	K	50	25	42	53	29	25	19
	Vol. (c.c.)	1,730	950	1,300	1,770	1,375	2,240	3,185
S. K.	*Serum*							
	Na	141	141	127	133	136	143	131
	Cl	107	102	90	93	96	91	96
	K	3.9	4.0	3.9	3.6	3.8	3.8	3.8
	CO_2	39	37	27	30	32	37	38
	Urine							
	Na	90	63	23	20	13	33	41
	Cl	54	78	33	36	48	31	29
	K	27	48	23	22	45	20	20
	Vol. (c.c.)	2,050	720	2,400	1,820	1,011	1,700	2,050
J. R.	*Serum*							
	Na	138	140	138	131	138	132	125
	Cl	113	106	97	98	98	95	98
	K	4.3	3.8	5.0	4.2	4.4	4.4	3.9
	CO_2	25	25	20	24	29	28	23
	Urine							
	Na	53	52	12	26	21	6	3
	Cl	56	60	43	44	48	27	37
	K	20	16	45	55	45	38	47
	Vol. (c.c.)	1,525	780	840	840	530	780	700
C. N.	*Serum*							
	Na	135	137	131	129	140	137	131
	Cl	102	100	87	95	105	102	101
	K	3.9	4.9	4.3	4.2	4.5	4.5	4.7
	CO_2	30	30	34	35	32	35	28
	Urine							
	Na	147	25	20	4	1	1	2
	Cl	157	47	12	16	6	4	7
	K	47	45	21	18	12	12	17
	Vol. (c.c.)	1,440	1,480	2,920	1,880	2,130	2,350	1,880
				"Hypertonic Saline" Group				
H. S.	*Serum*							
	Na	132	133	140	144	144	145	142
	Cl	101	98	104	107	106	97	106
	K	5.0	3.8	4.2	3.6	3.4	3.6	4.2
	CO_2	26	24	22	26	24	26	26
	Urine							
	Na	86	56	56	60	50	54	84
	Cl	100	94	82	122	89	63	93
	K	16	60	60	58	31	12	27
	Vol. (c.c.)	800	750	1,350	880	1,020	650	1,000

TABLE II—CONT'D

	MEQ./L.	PRE-OP.	OPER.	P.O. 1	P.O. 2	P.O. 3	P.O. 4	P.O. 5
W. K.	*Serum*							
	Na	138	141	139	138	139	134	135
	Cl	107	106	103	106	103	98	100
	K	4.0	4.0	4.3	4.4	3.8	3.4	3.9
	CO_2	27	24	26	27	23	37	23
	Urine							
	Na	36	41	68	51	73	66	72
	Cl	33	66	110	106	65	42	40
	K	23	54	83	95	14	11	11
	Vol. (c.c.)	1,610	1,050	400	550	1,300	2,850	2,450
O. M.	*Serum*							
	Na	128	138	142	140	140	141	133
	Cl	104	100	95	96	102	89	98
	K	4.3	3.8	3.7	3.9	3.3	3.6	4.6
	CO_2	23	25	24	26	23	22	27
	Urine							
	Na	37	47	75	56	39	35	30
	Cl	45	119	129	105	85	44	37
	K	27	60	61	37	39	16	16
	Vol. (c.c.)	860	800	1,400	1,200	550	1,300	750
L. S.	*Serum*							
	Na	138	140	139	134	136	137	142
	Cl	104	112	101	101	103	100	97
	K	3.8	4.0	4.0	3.9	3.6	3.6	4.2
	CO_2	23	26	38	24	28	26	27
	Urine							
	Na	61	63	91	72	44	91	63
	Cl	74	79	97	110	63	111	74
	K	27	35	45	34	36	45	30
	Vol. (c.c.)	1,250	1,200	350	1,400	1,100	850	525
C. M.	*Serum*							
	Na	148	135	130	138	139	138	144
	Cl	108	101	96	96	98	101	99
	K	4.5	4.5	4.0	3.9	4.2	5.6	4.0
	CO_2	29	29	31	25	30	31	28
	Urine							
	Na	89	105	36	20	13	36	105
	Cl	91	91	56	49	36	41	81
	K	16	112	24	17	16	12	27
	Vol. (c.c.)	2,450	600	3,750	3,500	1,850	2,750	1,750

No special evaluation of the renal status of the patients in this study was obtained, other than the routine urinalysis and NPN, which were within normal limits.

General endotracheal anesthesia of ether-nitrous oxide-pentothal was used for the majority of patients. Two did not receive ether, and one received cyclopropane.

All patients in this study were adult white males who had a thoracotomy plus a pulmonary resection. Pneumonectomy patients were excluded. The two groups were comparable with regard to age and magnitude of surgical procedure.

Table I lists the age, operative procedure, and pathology encountered in patients of each group.

RESULTS

The clinical course of the patients in both groups was comparable and uneventful during the period of the study. No evidence of peripheral or pulmonary edema or of hypertension was noted.

The serum and urinary electrolyte concentrations of patients in the "Control" and "Hypertonic Saline" groups may be seen in Table II. In Fig. 1, the comparative values of sodium in milliequivalent per liter, urinary sodium excretion in milliequivalent per 24 hours, and 24-hour urinary volume are depicted graphically. The graph represents the average of each group for a given determination.

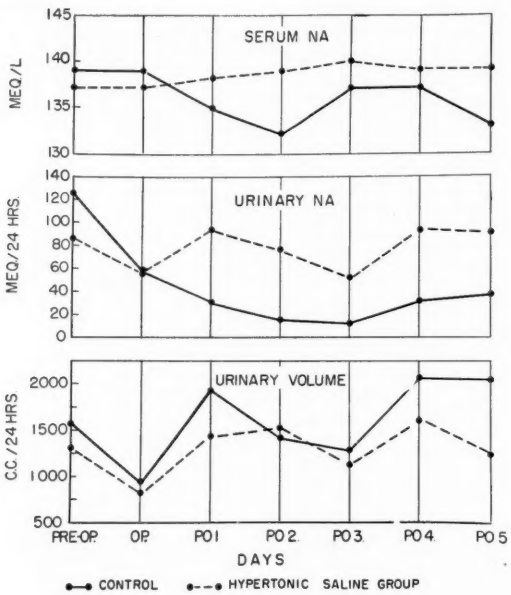

Fig. 1.

Because 24-hour urine collections were from 7 A.M. to 7 A.M., and since surgery in all patients was started at 1 P.M., the serum electrolyte levels on the day of operation represent preoperative values, and the 24-hour urine volume for this day actually consists of a combination of a 12-hour preoperative and a 12-hour postoperative specimen. Therefore, little variation of values in the two groups was seen during this period.

Sodium.—In the "Control" group, the markedly diminished urinary sodium excretion is seen to be associated with a postoperative hyponatremia. This is in agreement with other similar series previously reported.[3, 4, 6, 10, 11, 12, 17]

The urinary sodium excretion of the "Hypertonic Saline" group is well within the normal range as reported elsewhere[13, 17] and as compared with preoperative values. Serum sodium concentrations in this group did not exhibit

the characteristic postoperative depression. Rather wide variation in individual values were noted but, in general, a decrease in serum sodium concentration resulted in diminished urinary sodium excretion. These variations may be partially or wholly explained on the basis of individual differences in weight, body surface area, type of oral fluid intake (milk, broth, etc., versus water), degree of anorexia, and amount of sodium ingestion prior to operation.

Chloride.—Urinary chloride excretion roughly parallels that of sodium. However, in contradistinction to previous reports,[11, 12] the urinary chloride concentration is almost always greater than the sodium concentration in both groups. Serum chloride levels remained in the normal range, but tended to be lower in the "Control" group.

Potassium.—Potassium excretion shows a similar pattern in the two groups, with approximately double the preoperative excretion during the first postoperative day, then a return toward normal levels. Total urinary potassium loss during the period of study averaged 371 mEq. in the "Control" group and 330 mEq. in the "Hypertonic Saline" group. There is an apparent tendency for the loss in the "Control" group to be more sustained.

It is interesting that the urinary potassium excretion exceeds that of the urinary sodium in the "Control" group, while the converse is true in the "Hypertonic Saline" group.

Serum potassium levels are within normal limits, but tend to be slightly lower in the "Hypertonic Saline" group.

Carbon Dioxide Combining Power.—The carbon dioxide combining power remained within normal limits in both groups.

Urinary Volume.—The urinary volume of the "Control" group generally exceeded that of the "Hypertonic Saline" group, but the average volumes were roughly comparable.

SUMMARY

1. Studies of serum electrolytes (notably sodium) and urinary electrolyte excretion were carried out on thoracic surgical patients divided into two groups:

a. "Control" Group.—Those receiving 'routine' management, i.e., sodium restriction during the early postoperative period.

b. "Hypertonic Saline" Group.—Those receiving hypertonic sodium chloride solution postoperatively.

2. Thoracic surgical patients were chosen for this study because of minimal alteration of gastrointestinal tract function with only short-term dependence on parenteral feeding.

3. The results indicate that the postoperative kidney can and does excrete sodium when serum sodium levels are maintained by administration of hypertonic sodium chloride solution.

4. The difference in urinary chloride excretion in the two groups was of a magnitude comparable to that of sodium. In addition, the urinary chloride excretion generally exceeded the urinary sodium excretion.

5. Little difference was noted in urinary potassium excretion when comparing the two groups, except that it exceeded the urinary sodium concentration in the "Control" group, while the converse was true in the "Hypertonic Saline" group.

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ANATOMIC AND PATHOLOGIC STUDIES OF THE THORACIC DUCT

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ALTHOUGH various portions of the lymphatic system were known to the ancients, it was not until the mid-seventeenth century that the anatomy of the right lymphatic trunk and of the thoracic duct was clarified. More recently, further studies of the thoracic duct system have been made; however, some divergence of opinion apparently still exists concerning the detailed anatomy of this structure. Similarly, with regard to pathologic processes affecting the thoracic duct, only a meager number of articles on the subject are to be found.

In view of the foregoing, coupled with recent interest in the surgical management of injuries to the thoracic duct and chylothorax, the present study was undertaken in an effort to gain additional information concerning the anatomy and pathology of the thoracic lymphatic system.

MATERIALS AND METHODS

Sixty fresh cadavers were utilized at post-mortem examination. In 50 instances, the thoracic duct was exposed from the right side just above the diaphragm and divided. The proximal and distal ends of the divided duct were then cannulated with small plastic catheters and injected with 50 per cent sodium iodide solution following which radiographic exposures in anteroposterior projection were obtained. It was found necessary to ligate the left innominate vein prior to injection to prevent rapid filling of the superior vena cava, azygos vein, right auricle, inferior vena cava, and hepatic veins, since filling of these structures made radiographic interpretation of the thoracic duct system difficult. Following radiographic exposure, 1 per cent methylene blue solution was injected through the catheters in a similar manner resulting in rapid staining of the duct system and thus facilitating dissection and removal of the entire duct and cisterna chyli (Fig. 1). Subsequent to the above macroscopic observations, portions of the duct were opened longitudinally and, after inspection, multiple sections from various levels of the duct were removed for histologic study. In addition to routine hematoxylin and eosin preparations, Verhoeff and Van Gieson stain techniques were employed. In 10 additional cases, retrograde injection from the cervical termination of the duct was attempted, but in these cases no further examination of the thoracic duct was performed.

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Of the 50 cases studied extensively, age at death was as follows: First, third, and fourth decades, one each; fifth decade, 7; sixth decade, 5; seventh decade, 14; eighth decade, 11; ninth decade, 10. Ages ranged from 9 to 89 years. Carcinoma was present and was the major cause of death in 13 cases. Of the remainder, degenerative cardiac, renal, and hepatic diseases were most commonly the cause of death. Death from overwhelming sepsis of the thoracic or peritoneal cavities was not encountered.

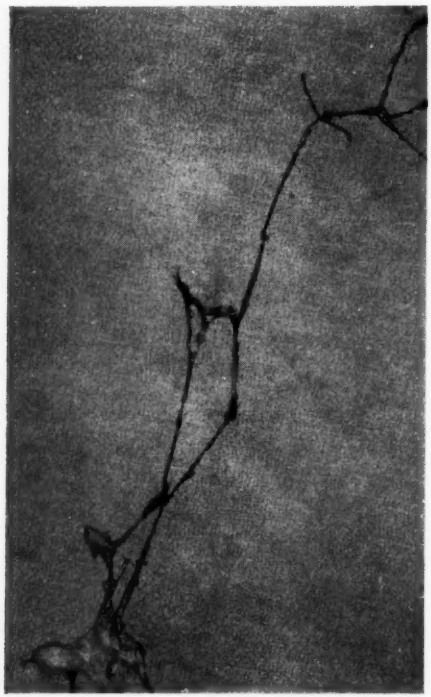

Fig. 1.—Cisterna chyli and entire thoracic duct dissected from a 78-year-old woman who died of generalized arteriosclerosis and terminal bronchopneumonia. Two major trunks in the lower thoracic portion are demonstrated.

FINDINGS

The common gross anatomy of the thoracic duct was again reaffirmed. The cisterna chyli showed considerable variation in size and outline but usually was globular, measured 3 to 4 cm. in length and 2 to 3 cm. in diameter. In 26 instances it overlaid the first and second lumbar vertebrae and in one instance extended from the twelfth thoracic to the third lumbar vertebrae. In no case was it found to extend below the third lumbar vertebra, and in only 2 instances did it extend cephalad as far as the tenth thoracic vertebra. In one instance the cisterna was completely absent. The thoracic duct was an essentially single

Fig. 2.—Representative examples of contrast radiographic studies.

A, A 67-year-old woman who died of acute pancreatitis. The duct is single throughout the chest.

B, A 71-year-old man dying of arteriosclerotic heart disease. Two major trunks and adjacent collaterals in the mid-thorax. The aorta is heavily calcified throughout its course as is a portion of the pericardium. This does not represent extravasated dye.

C, A 25-year-old man who died of a head injury. The duct has two major trunks in the lower chest.

D, A 62-year-old man who died in diabetic coma. The duct has multiple channels from T_6 to T_{10}.

trunk in 18 cases; single to the mid-thorax when it consisted of multiple trunks, in 17 cases; and with double or multiple channels at and below the level of the tenth thoracic vertebra in 14 cases. Drainage into the jugular-subclavian veins was totally left sided in all but one case. (These findings are demonstrated and summarized in Figs. 2 and 3). Usually the duct had a beaded appearance because of dilatation cephalad to each set of valves (Fig. 4) which were found every 4 to 8 cm. apart, being uniformly present in the terminal portions of the duct and in decreasing frequency in the upper thoracic portion and generally absent below the sixth thoracic vertebra. In 10 instances, retrograde injection of the duct was attempted by cannulation of the duct at its cervical termination, but the unidirectional valves uniformly prevented retrograde filling beyond the first or second thoracic vertebrae, and with an increase in injection pressure, rupture of the duct proximal to competent valves occurred, confirming similar observations by others.[1, 2]

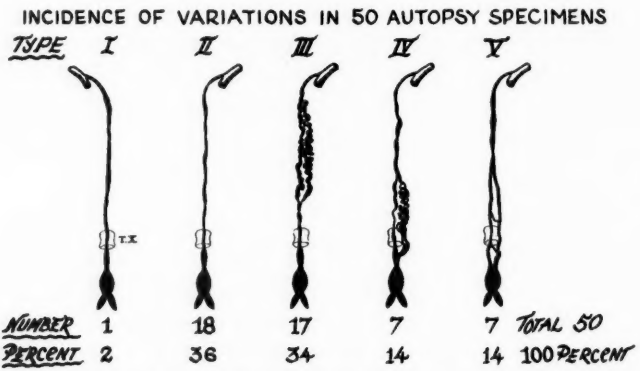
INCIDENCE OF VARIATIONS IN 50 AUTOPSY SPECIMENS
TYPE I II III IV V
TX
NUMBER 1 18 17 7 7 TOTAL 50
PERCENT 2 36 34 14 14 100 PERCENT

Fig. 3.—(Anatomy of the Thoracic Duct.) Chart demonstrating five major gross anatomic variations observed and their rate of occurrence.

In all specimens, portions of the duct were opened longitudinally and gross inspection performed. Even though 21 of the 50 cases were over 70 years of age, the duct retained considerable elasticity, the intimal surface was smooth and white and, although on occasion a few gray-white, waxy, intimal plaques were observed, no yellow atheromata were found in any of the specimens. In 3, metastatic tumor was grossly present in the duct but no unusual dilatation of the duct or chylus effusion was demonstrated at necropsy. In one additional case, metastatic tumor in the duct was recognized only on microscopic examination.

On histologic examination the thoracic duct differed in structure from similarly sized veins in that the thoracic duct was a more muscular vessel and the layers of the wall were less sharply defined. Such loss of definition of the layers was more marked in the terminal portion than at lower levels where better definition of the layers was observed (Fig. 5). The intima was lined by a single layer of flat endothelial cells whose oval nuclei paralleled the long axis

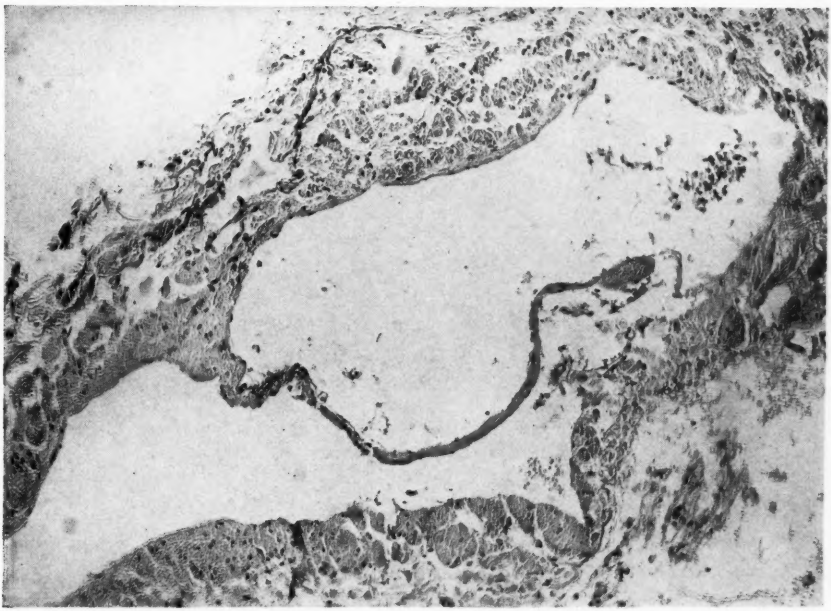

Fig. 4.—Valve leaflet showing characteristic proximal sacculation of the thoracic duct wall. (H. and E. ×130; reduced ⅙.)

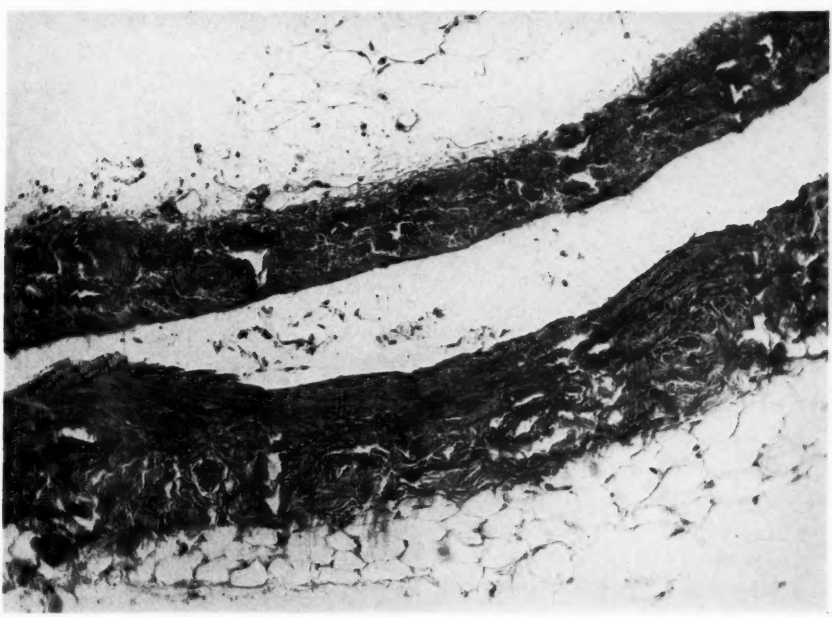

Fig. 5.—Normal thick muscular wall of distal thoracic duct. (Verhoeff-Van Gieson ×130; reduced ⅙.)

of the duct. Subjacent to the intimal cells was a sharply defined elastic layer separating the endothelial cells from the supporting thin layer of fibroelastic tissue in which a number of longitudinally arranged smooth muscle fibers were found. The intima was limited by a reasonably well-developed internal elastic membrane. In the proximal portions of the duct, the numbers of smooth muscle fibers in the intima diminished and the entire thickness of the intima was reduced. In the distal portions of the duct, the media was well defined, composed of an inner circular and an outer longitudinal or oblique layer of smooth muscle supported by delicate fibroelastic tissue. The thickness of the media also decreased proximally, mainly from a reduction of longitudinal muscle fibers. The adventitia tended to be poorly defined, the innermost portion being composed of dense collagenous fibers oriented longitudinally interspersed with scattered elastic fibers and some longitudinal muscular fibers. The outer portion of the adventitia consisted of loose fibroadipose tissue blending with the surrounding tissues.

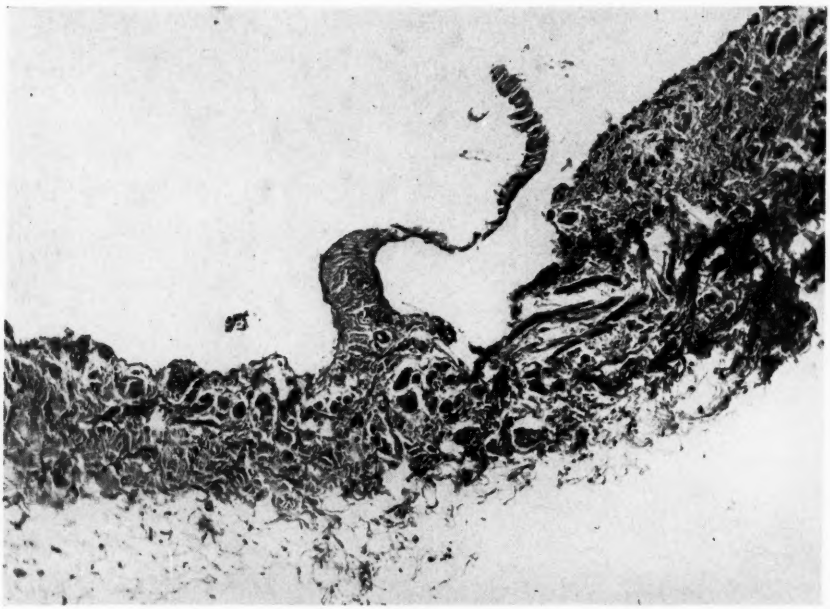

Fig. 6.—One of the tricuspid valve leaflets. Muscle fibers are present in the base of the valve. (Verhoeff-Van Gieson ×130; reduced ⅙.)

The duct was richly supplied by small capillaries which entered at right angles to the long axis and appeared to penetrate to the inner portion of the media. The valves described grossly were merely folds of intima which on occasion contained a few muscle bundles (Fig. 6).

Moderate sclerosis of the wall of the duct was manifested by the development of waxy, slightly raised intimal plaques. These plaques resulted from

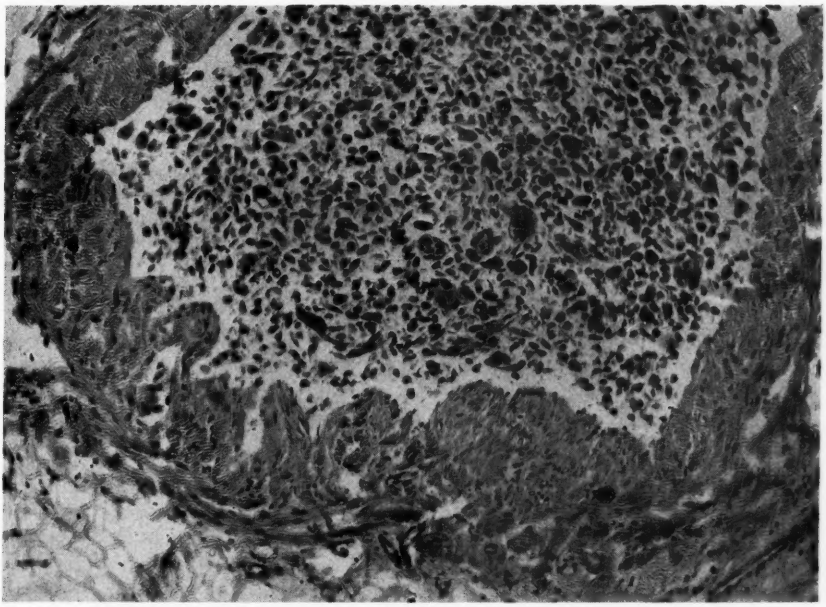

Fig. 7.—Anaplastic bronchogenic carcinoma in the lumen of the thoracic duct. The duct wall shows no changes. (H. and E. ×130; reduced ⅙.)

Fig. 8.—Neoplastic cells within thoracic duct from spindle cell carcinoma of the bladder. (H. and E. ×130; reduced ⅙.)

splitting and reduplication of the elastic fibers, fibrosis, and hyalinization in the intima. Scarring of muscle in the media was also observed. Many of the supporting capillaries in the adventitia showed intimal proliferation and hyalinization of their walls with condensation of elastic fibers.

In those instances where neoplastic involvement of the duct was observed, the tumor infiltrated the entire thickness of the wall, resulted in neoplastic mural thrombi or presented as free nests of neoplastic cells in the duct lumen (Figs. 7 and 8).

DISCUSSION

Embryologically, the thoracic duct originates in the abdomen at the cisterna chyli in the form of paired ducts which pass cephalad through the thorax. The right duct crosses to the left, dorsal to the aorta, at about the level of the fourth thoracic vertebra and unites with the caudal downgrowth of the left jugular lymph sac. The right jugular lymph sac develops to form the less extensive right lymphatic trunk, and the embryonic left thoracic duct, which in the embryo communicates freely with the embryonic right thoracic duct forming a lymphatic plexus along the course of the aorta, becomes obliterated in the majority of instances resulting in an essentially single duct in the thorax (the embryonic right duct) which crosses to the left terminating in the left jugular vein. This distribution pertains in the human being and most mammals; however, in birds, a bilaterally symmetrical duct system is retained. Davis[1] felt that the variations in thoracic duct anatomy were predictable on an embryologic basis and, moreover, resulted from failure of the usual developmental pattern to progress in the usual manner.

It is felt that such an explanation for the variations noted is more in keeping with the observations reported than to ascribe such variations to acquired processes. In the present series, no evidence of inflammatory changes in the duct was noted and of the 50 patients studied 13 had died of carcinoma, yet of the patients with double ducts observed at diaphragmatic level (Types IV and V, Fig. 3.) only one had carcinoma. The remaining 13 cases of carcinoma were equally represented in Types II and III.

The gross anatomic findings in this study, based upon both contrast radiographic survey and dissection, suggest that the usual variations noted fall into five general groups and of surgical significance is the finding that 28 per cent of cases have two or more ducts at diaphragmatic level which is in sharp contrast to the findings of some,[2, 3] yet in essential agreement with the findings of others.[1, 4] Our findings suggest that such variations are not secondary to inflammatory or neoplastic disease but depend upon aberration during embryonic development.

Concerning pathologic processes affecting the thoracic duct, a survey of the literature yields few articles. Enzmann[5] reviewed the subject in 1883 and Sindoni[6] again in 1939. Essentially, three types of lesions have been described. (1) inflammation, characterized by lymphangitis and perilymphangitis, always secondary in pathogenesis, and usually the consequence of fulminating infection primary in the thorax or abdomen; (2) cystic or aneurysmal dilatation of the duct, and (3) malignancy. As previously mentioned, no inflammatory changes

involving the duct were observed in the present study which is understandable in that none of the necropsy subjects were found to have significant thoracic or peritoneal infection. Also, cystic dilatations of the duct were not observed; however, such lesions are extremely rare and necropsy descriptions of only 10 such lesions were found in the literature[6, 11] and 4 additional lesions which were surgically resected.[7-10] Various theories concerning the origin of such cysts have been postulated, among which infection, atherosclerosis with associated degenerative changes, and obstruction of the duct have been considered to play a significant role. It is felt that such explanations have little merit in that many of the reported cases occurred at a relatively young age, significant infection and inflammatory changes are not apparent in the clinical protocols and, finally, only in the case reported by Kelbling[11] was a true atherosclerotic plaque described. It is suggested that such lesions are most likely lymphangiomata and probably of congenital origin. In the present series, the histologic changes observed in the duct indicate that this vessel does undergo a type of sclerosis not dissimilar to the aging changes observed in peripheral veins. Although the duct transports about 70 per cent of the absorbed fat from the intestinal tract, no atheromatous changes were observed, and if atherosclerosis does occur it must be exceedingly uncommon.

Primary malignancy of the thoracic duct has apparently never been demonstrated, in contradistinction to metastatic involvement which has been recognized since the first description by Cooper in 1798.[12] Its occurrence was considered infrequent by both Enzmann[5] and Sindoni,[6] and Willis, in 1952, was able to find only 90 reported cases.[13] In his own series, Willis observed metastatic involvement of the thoracic duct in 18 of 500 cases of malignancy, an incidence of 3.6 per cent, which led him to conclude that such lesions were probably more frequent than previously thought. In 13 instances of malignancy among the 50 subjects studied in our series, 4 (30 per cent) demonstrated metastatic involvement of the thoracic duct. Our findings would thus tend to indicate an even higher occurrence than previously noted, which undoubtedly is a manifestation not of the rarity of such involvement but rather reflects the rarity of examining the thoracic duct on routine post-mortem examination.

The mechanism by which neoplastic cells involve the thoracic duct is of interest. Our cases suggest that direct extension of tumor through the duct wall from metastatic deposits about or contiguous with the duct does not occur. It is believed that the small lymphatic channels observed in the areolar tissue about the duct, and which undoubtedly drain into it, represent the portal of entry for such metastases into the duct wall itself. Although nests of metastatic cells could be observed within the lumen of the duct, with no evidence of involvement of the duct wall, these lesions cannot be construed as primarily embolic, since such a phenomenon is predicated upon the mechanism of tumor transport to the duct from another distant vessel. Such a concept is considered untenable. That fragments of tumor may break off from a lesion already established in the duct and come to lodge at a higher level appeals to us as the explanation for such occurrences. Retrograde extension of tumor

within the sheath of the duct could also account for these findings. In addition, the possibility of emboli from the duct to the blood stream via the jugular vein is apparent.

Chylothorax or chylous ascites were not observed in any of the subjects studied in this series; however, the often expressed concept that such effusions secondary to neoplasm are the result of obstruction of the duct system and its collaterals, or from extrinsic compression, deserves comment. That ligation of the thoracic duct at any level, both experimentally and clinically, has not resulted in chylous effusions is generally accepted and militates strongly against such a mechanism. In addition, it does not seem reasonable to believe that neoplasms can completely obliterate the thoracic duct system and all of the available collateral channels. In a previous article,[14] 2 cases of chylothorax secondary to extensive malignancy were reported. The duct system in both instances was readily injected and visualized roentgenologically at the time of surgery. Not ony was no obstruction of the thoracic duct demonstrable in either, but expanded collaterals were well demonstrated in one instance (Case 3, Ref. 14). It is felt that these observations are further confirmatory evidence against obstruction of the duct system as the cause of chylous effusion. That a limited localized lesion may, by extrinsic pressure, result in obstruction and the outpouring of chyle, as in a case reported by Brewer,[15] also seems unlikely. Brewer's case was apparently a neurofibroma partially overlying the cisterna and intimately attached to it. Photomicrographs reveal it to be unusually rich in lymphatic vessels and it is suggested that its growth caused rupture of such channels.

From the above observations it is felt that chylous effusions probably do not result from intrinsic or extrinsic obstruction of the major duct system or by metastatic block of the collateral bed, but rather result from actual perforation, tearing, or erosion of the wall of the duct or major collaterals by malignant invasion, and that continuing leak of chyle is a manifestation of the well-known propensity of neoplasm to retard and even prevent healing.

SUMMARY

The gross and microscopic anatomy of the thoracic duct studied in 50 autopsy subjects by contrast roentgenography, dissection, and histologic investigation is presented. The variations encountered are described and tabulated. Moderate sclerosis of the duct wall and secondary involvement by metastatic tumor were the only pathologic processes observed in this series and, these changes, as well as other morbid processes of the thoracic duct reported in the literature, are commented upon.

The authors wish to express their thanks and appreciation to Dr. Arthur W. Wright, Professor of Pathology, and Dr. John F. Roach, Professor of Radiology, Albany Medical College, for their assistance and cooperation in this project.

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DISCUSSION

(PAPERS BY MORRIS [PAGE 590], STATE [PAGE 599], HERRON [PAGE 609], CREAMER [PAGE 615], KAUSEL [PAGE 631] AND THEIR ASSOCIATES)

DR. AARON HIMMELSTEIN, New York, N. Y.—I would like to discuss Dr. State's paper, No. 18. We have been interested in bronchial blood flow and have made measurements in intact man, using the idea that lowering the arterial saturation would allow the arterial blood to pick up oxygen. If we do this and study the patient by bronchospirometry and cardiac catheterization, by appropriate manipulation, we can measure the bronchial blood flow. This is different from what Dr. State did, in that we measure the flow which reached a diffusing surface, whereas he measured the anatomic flow. In a patient who had a ligation of the pulmonary artery we were able to measure a flow of about 9 per cent of the total cardiac output. In a patient with congenital heart disease, in whom we later demonstrated that the pulmonary artery had no connection with the heart, we were able to measure 2.9 L. flow through collaterals. We have applied this technique in a variety of conditions, and have shown variations which depend upon the stress of the situation and on the anatomic problem. In carcinoma of the lung which obstructed the pulmonary artery, we were not able to show any collateral circulation to the lung, whereas in congenital heart disease we showed a maximum of collateral flow.

DR. PAUL NEMIR, JR., Philadelphia, Pa.—I rise to discuss the papers of Dr. Herron and Drs. Creamer and Olsen. I agree with Dr. Herron that some type of emptying procedure at the pyloroduodenal area should be done when performing an esophagocardiomyotomy for achalasia of the esophagus. We have performed a pyloromyotomy or pyloroplasty on approximately the last 15 patients upon whom we have done an esophagocardiomyotomy. We have now had the opportunity to follow some of these for as long as 2½ years and, while the series is certainly too small to allow any definite conclusions, the incidence of serious complications has been less in this group of patients. If one assumes that the difficulty in achalasia is due to some derangement of the intrinsic neural mechanism at the esophagocardiac junction, it seems reasonable to assume also that this same derangement might also be present in the intrinsic neural mechanism at the pyloroduodenal junction. A delay in emptying at the pyloroduodenal area has been noted in some of our earlier cases and I am sure that this delay in emptying is a contributory factor in regurgitation esophagitis.

I want to congratulate Dr. Creamer and Dr. Olsen and their associates for the fine work which they have done. Our findings along the same lines of investigation have been essentially similar. (slide) Occasionally the widely dilated esophagus may decrease in size following operation. For example, here is a film of a 72-year-old woman with symptoms of achalasia of approximately one year's duration. Note that the very widely dilated tortuous esophagus in the preoperative film has decreased to a fairly respectable size only 6 weeks after operation.

(slide) Although the size of the esophagus on roentgen study was rather markedly decreased, and although the patient was entirely free of her dysphagia, note in this slide that there has been absolutely no change in the motility pattern of the esophagus. There is still the same unrhythmicity, the same decrease in the amplitude and frequency of contractions. There is, however, some decrease in the resting tone at the esophagocardiac junction. From the pathophysiologic standpoint, it seems to me of little importance whether the functional obstruction in the esophagocardiac area is on the basis of a tonic spasm of the inferior esophageal sphincter or a failure of relaxation of that muscle. Under either circumstance, it seems to be satisfactorily relieved by an esophagocardiomyotomy.

DR. R. E. TABER, Detroit, Mich.—It is difficult to add anything to the beautiful presentation you have just heard. I would like to show a few slides on some work that was begun in 1951 and published 2 years ago. It demonstrates a different result and lends support to the value of cardioesophageal myotomy. Here we see esophageal motility studies on 3 patients with severe cardiospasm who preoperatively were shown to have a complete lack of esophageal contractions. Below we see motility studies on the same 3 patients performed on an average of 18 months postoperatively following myotomy. I believe it is evident that there has been a striking return of esophageal contractions. Dr. Olsen did not mention how long postoperatively his studies were done.

(slide) Here again we see the same sort of thing; the preoperative esophageal ileus and response to Urecholine, and 15 months postoperatively there has been a marked return of motility pattern. I will say, however, that I agree with Dr. Olsen that these contractions, when they re-appear postoperatively, are disorganized.

DR. JOSEPH A. WEINBERG, Long Beach, Calif.—I wish to direct my remarks to Paper No. 22; the studies on the thoracic duct. We must all be very much impressed by the excellent studies of Dr. Kausel and his group. I would like to ask Dr. Kausel if, in their studies with the dyes and roentgenograms, they discovered tributaries going into the thoracic duct from, say, the mediastinal region. I think it would have considerable importance in throwing some light upon the possible spread of cancer by way of the thoracic duct and then the general blood circulation. Also, there is considerable significance in the multiple openings of the terminal part of the duct into the venous system. Scalene node biopsies particularly invite the possibility of injury to terminal radicals of the thoracic duct. The fact that the thoracic duct usually has multiple exits into the venous system makes surgical injury less serious, since if one radical of exit is interrupted, others will continue to function.

THE STUDY OF VENTRICULAR FIBRILLATION BY THRESHOLD DETERMINATIONS

NORMAN E. SHUMWAY, M.D.* (BY INVITATION), JOHN A. JOHNSON, PH.D. (BY INVITATION), AND RICHARD J. STISH, B.E.E. (BY INVITATION)
MINNEAPOLIS, MINN.

THE purpose of this paper is to introduce a method for the quantitative study of ventricular fibrillation. Recent progress in open heart surgery has brought this arrhythmia sharply into focus. Unfortunately, investigation of various fibrillatory and antifibrillatory states, both physical and chemical, has been poorly systematized and incompletely developed.

Although ventricular fibrillation is a diffuse and complex phenomenon, it does yield to scientific examination. In 1940, Wiggers[1] described a technique for measuring ventricular fibrillation thresholds. This important work has been largely neglected by heart surgeons except as it pertains to defibrillation. Most of the present literature concerning defibrillation of the ventricles is a reiteration of Wiggers' contributions.[2] Physiologists, notably Brooks, Hoffman, Suckling, and Orias,[3] have studied cardiac excitability in great detail with precision, electronic instruments. Because of the complexity of the heart, results have always been short of standards set by neurophysiologists in their studies of nerve preparations; nonetheless, valuable quantitative data have accumulated with respect to the excitability cycle of the heart, a subject examined first by Bowditch in 1871.[4] The combination, then, of threshold measurements and modern electronic instrumentation should provide for ventricular fibrillation the same, sound quantitative basis now claimed for cardiac excitability.

A variety of methods has been used to examine ventricular propensity to fibrillation. We submit that the only quantitative approach is that which utilizes ventricular fibrillation thresholds. Single, rectilinear shocks of known and graduated strength applied directly to the heart surface at the same instant in successive cardiac cycles constitutes the method of choice. Weak, subthreshold shocks are followed by stimuli of increasing current until fibrillation intervenes. Each stimulus is a single electric shock whose current strength must be accurately measured. The duration of stimulation is another factor requiring absolute control. Ten milliseconds is a convenient time limit for each shock. Stimuli of increasing current strength are not comparable

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*This work was done during Dr. Shumway's tenure as a Special Trainee of the National Heart Institute.

unless each shock is delivered at the same point in the cardiac cycle. Wiggers and Wegria[5] showed that stimuli applied during the rise of intraventricular pressure are without effect and that maximal vulnerability to ventricular fibrillation is in late systole, a period reflected by the T wave of the electrocardiogram. The final 30 to 90 milliseconds of systole is the vulnerable period. Why a vulnerable period exists at all can be explained, perhaps, by the asynchronous arrival of the myocardial fibrils at diastolic thresholds with the result an aggregate of cells in varying stages of electrical instability. In our experiments, each stimulus was delivered during the vulnerable period of the heart cycle by means of a signal-synchronization circuit triggered by the R wave of the electrocardiogram.

The criteria which must be satisfied by a group of shocks provocative of ventricular fibrillation before any comparative analysis may be permitted are as follows: the current must be measured, the duration of stimulation must be the same for all shocks, and each stimulus must consist of a single shock delivered during the vulnerable period late in systole.

METHOD

Adult mongrel dogs of either sex weighing from 8 to 20 Kg. were subjected to left thoracotomy through the fifth intercostal space. Intravenous sodium pentobarbital provided the anesthesia, and all animals were ventilated with 100 per cent oxygen by means of an electronic respirator. The usual duration of the experiments was 6 hours; hence, additional anesthesia was given as needed but only in 50 mg. amounts. The state of anesthesia, therefore, was reasonably constant, and no particular influence of the anesthetic level could be detected on ventricular fibrillation thresholds. No appreciable change was noted in rectal temperatures with the chest open for several hours.

After a longitudinal incision was made in the pericardium, the heart was suspended by means of pericardial suture to the muscular borders of the thoracotomy. The conventional vertical sternotomy incision was used in early experiments, but exposure of the left ventricle, especially posteriorly, was inadequate. Left lateral thoracotomy provided simultaneous visualization of the right ventricle and the anterior and posterior aspects of the left ventricle without manipulation of the heart. Rigid surgical technique was observed in preparation of the heart so that physiologic departures were minimized. All animals responded well at the conclusion of the experiment and appeared capable of survival. The experiments were acute, however, and survival was not sought.

Repetitive stimuli were not applied precisely to the same points in a test field because of charring of the cardiac surface. Threshold values registered over burned myocardium were fictitiously high due to short circuiting of the current between the electrodes. A certain amount of freedom was justified with respect to placement of the stimulating electrodes because of the relatively large test areas available. The interval between threshold determinations varied but corresponded in general with the period of time needed for

complete recovery of the heart as monitored by the electrocardiogram. The common interfibrillatory rest period was 5 to 15 minutes. Retrieve from the fibrillatory state was uniformly accomplished by electric countershock in 5 to 7 seconds. Massage was not administered; drugs were never given. As many as 50 determinations were obtained in some preparations.

The current in milliamperes just adequate to provoke ventricular fibrillation of at least 2 seconds' duration was interpreted as having threshold strength. Spontaneous defibrillation occurred frequently within the 2-second limit but only rarely after 2 seconds. Production of a burst of ventricular extrasystoles was never accepted as the equivalent of ventricular fibrillation; such a compromise would seriously distort the results because several milliamperes often separated the shock provocative of extrasystoles from that capable of initiating ventricular fibrillation. Test shocks were delivered every 6 to 10 beats, and a shock of given amplitude was repeated at least three times before the current was increased. In experiments where a coronary artery was occluded, one minute of occlusion was permitted to elapse before stimulation; spontaneous fibrillation did not occur with sufficient frequency to interfere with these experiments.

The heart rate throughout was that determined by the physiologic processes of the animal. No effort was made to drive the heart at a fixed rate. Serious errors in cardiac excitability experiments have been attributed to the use of driving electrodes.[6]

INSTRUMENTATION

Fig. 1 is a schematic diagram of the instrumentation.

The electrocardiogram of the animal under study was recorded on one channel of a Sanborn Twin-Viso Cardiette.* A modified Lead II configuration of subcutaneous electrodes provided a consistently good display of cardiac potentials.

The amplified electrocardiogram potentials were fed into a triggering circuit whose output was coupled to the synchronizing input of a Grass stimulator.† The output of the stimulator was connected to a bipolar electrode constructed of 2 mm. silver wires with polished hemispherical tips and one centimeter separation. The anodal lead to the electrode contained a 5,000 ohm resistor to minimize the effects of changing electrode resistances. The magnitude of the current delivered to the electrode is obtained by observing, with a cathode ray oscilloscope,‡ the voltage drop produced across a precision 10 ohm resistor placed in the cathode lead of the electrode system. A permanent record of current magnitude was obtained by recording the same voltage on the second channel of the Sanborn Twin-Viso.

The electrocardiogram was also displayed on a second cathode ray oscilloscope. The stimulator output was applied to the Z axis of this oscilloscope;

*Model 60, Sanborn Twin-Viso Cardiette, Sanborn Co., Cambridge, Mass.
†Model S-4-B Stimulator, Grass Instrument Co., Quincy, Mass.
‡DuMont Type 304-A cathode ray oscillograph.

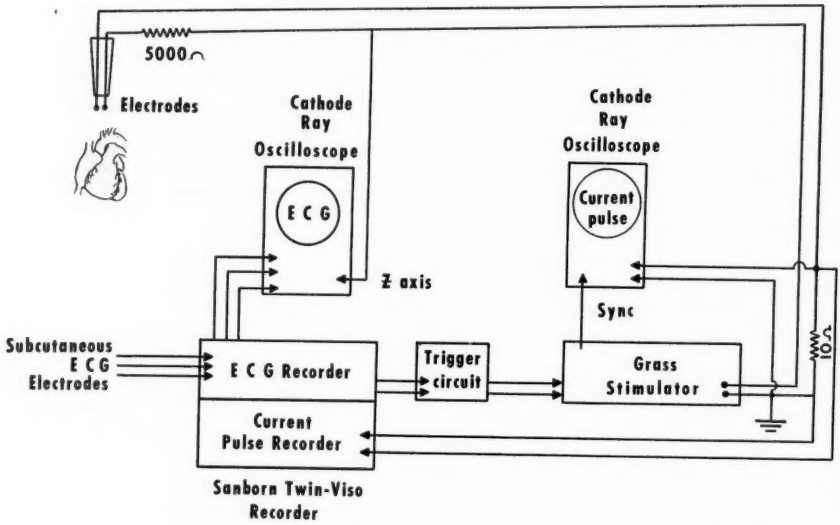

Fig. 1.—Block diagram of apparatus for ventricular fibrillation threshold determinations.

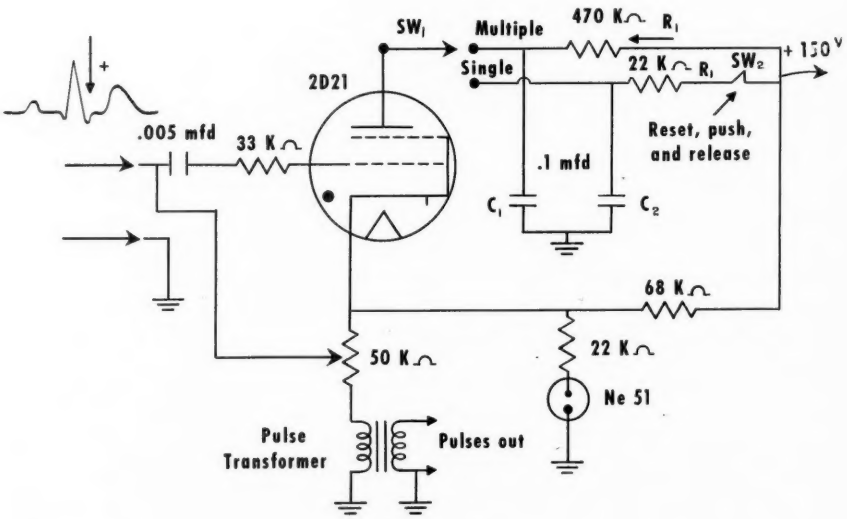

Fig. 2.—Trigger circuit.

brightening of the trace at the moment of stimulation provided a very simple and direct method of monitoring the position of the stimulus in the cardiac cycle.

The array of instruments just described permitted all necessary data to be read directly from the cathode ray oscilloscopes or to be recorded on the Sanborn at the option of the operator.

The trigger circuit, detailed in Fig. 2, provided several important functions and served well its primary responsibility of finding the vulnerable period: (1) a uniform synchronizing pulse was given both to the stimulator and to the current monitoring cathode ray oscilloscope, (2) a single synchronizing pulse was provided for the stimulator upon the occurrence of the first R wave after the reset button was released, and (3) a synchronizing pulse could be provided for each cardiac cycle, a feature of great importance during preliminary adjustment of the equipment.

Production of a synchronizing pulse was achieved by the discharge of a capacitor (C_1 or C_2) through a pulse forming transformer. The thyratron (Type 2D21) served as a switch and allowed the capacitor to discharge on the downward portion of the R wave of the electrocardiogram. When the switch (SW_1) was set for multiple pulses, the series resistor (R_1) extinguished the thyratron and allowed C_1 to recharge between successive R waves. In the single pulse mode of operation the thyratron continued to conduct after being triggered by the R wave, thereby preventing capacitor C_2 from recharging, thus, the formation of synchronizing pulses by succeeding R waves could not occur. This insensitive state was terminated manually by opening the reset switch (SW_2) which extinguished the thyratron. Closing the reset switch allowed capacitor C_2 to charge, a state it retained until the thyratron was triggered by an R wave.

CORONARY OCCLUSION EXPERIMENTS

To examine the precision of this method, ventricular fibrillation thresholds were determined over infarcted myocardium and compared with controls before coronary occlusion and after coronary disocclusion. A separate set of controls was comprised of threshold values taken elsewhere on the left ventricular surface than on the infarct.

In the initial series of coronary occlusion experiments, the circumflex ramus of the left coronary artery was dissected free near its origin. Ventricular fibrillation thresholds were determined with stimuli delivered on the cardiac areas supplied by the circumflex vessel first without occlusion, then with occlusion. Thresholds with stimuli applied away from the circumflex area were also compared with and without coronary occlusion. The order of procedure was varied frequently. Fig. 3 shows a fibrillation threshold in a typical experiment with stimuli applied on the infarct with the circumflex artery occluded. The first shock is of 8 Ma. strength, the second 10, and the threshold 11.5 Ma. Each shock was delivered during the vulnerable period just before the peak of the T wave. In general, the ascending limb of the T wave was the period of lowest threshold value. Fig. 4 graphically portrays the results of this series. Standard

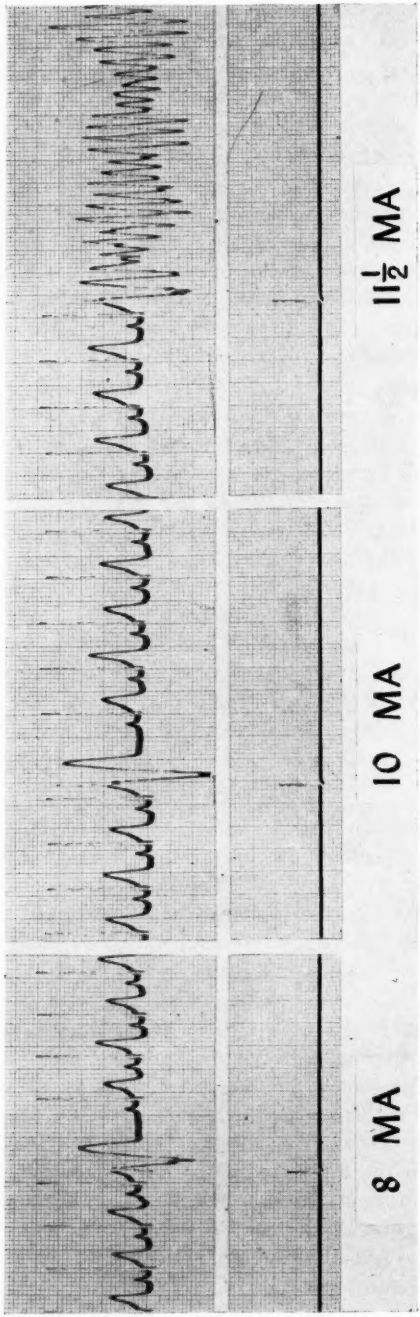

Fig. 3.—Stimuli applied on the infaret with the left circumflex coronary artery occluded. Note that each shock falls at the same point in the cardiac cycle.

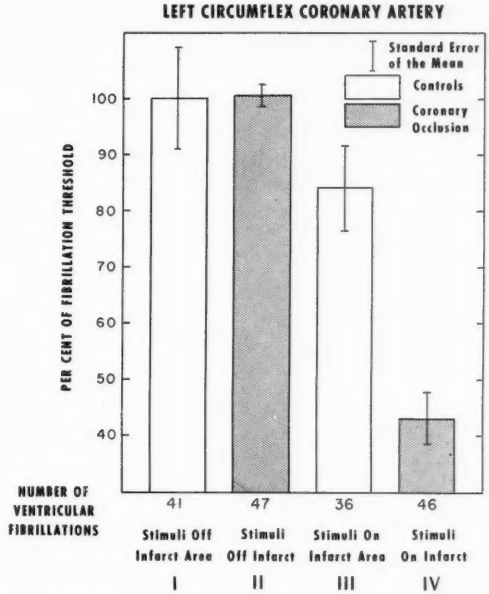

Fig. 4.—Column I is set at 100 per cent, and each of the other columns is calculated in per cent of column I.

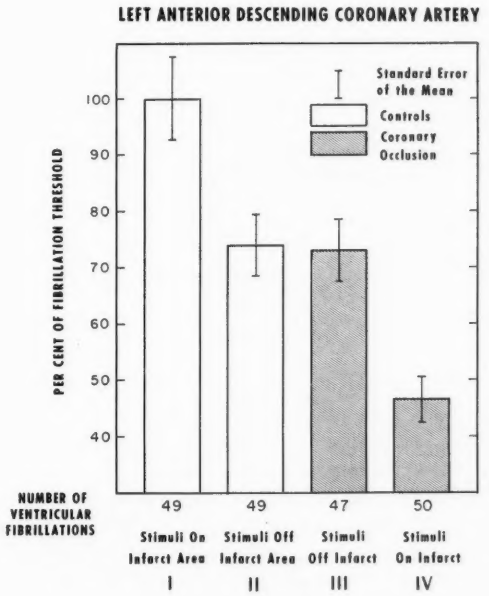

Fig. 5.

errors of the mean are shown. Assuming the null hypothesis, the probability that columns III and IV are drawn from the same population is less than one chance in 100. No statistical difference can be detected between columns II and III. I and II are nearly identical.

In the second group of coronary occlusion experiments, the same procedure was followed except that the anterior descending branch of the left coronary artery was used. Again, thresholds were determined with stimuli applied on and off the area of distribution of the anterior descending artery with and without occlusion. Fig. 5 shows the results and standard errors of the mean.

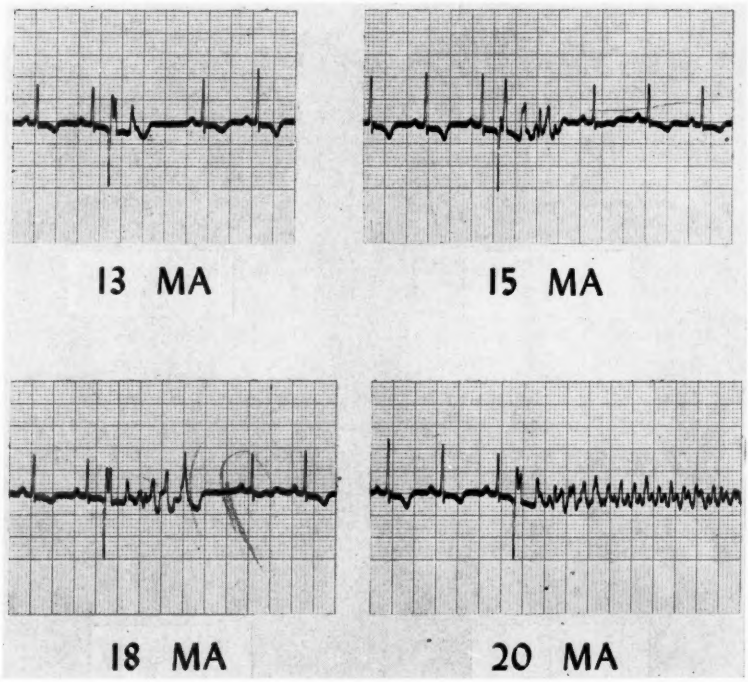

Fig. 6.—Stimuli applied over the posterior portion of the left ventricle. Current read from oscilloscope.

The probability that columns III and IV represent the same population is less than one chance in 100. Columns II and III are similar, and now a statistically valid separation is beginning to develop between columns I and II, or I and III; the probability of chance is two to five in 100.

From these two sets of coronary occlusion experiments some interesting conclusions seem warranted. Ventricular fibrillation thresholds are significantly lower during coronary occlusion if stimuli are applied directly on the infarct; this is in accord with the work of Wiggers, Wegria, and Pinera.[7] If stimuli are applied away from the infarct, however, no diminution in threshold can be

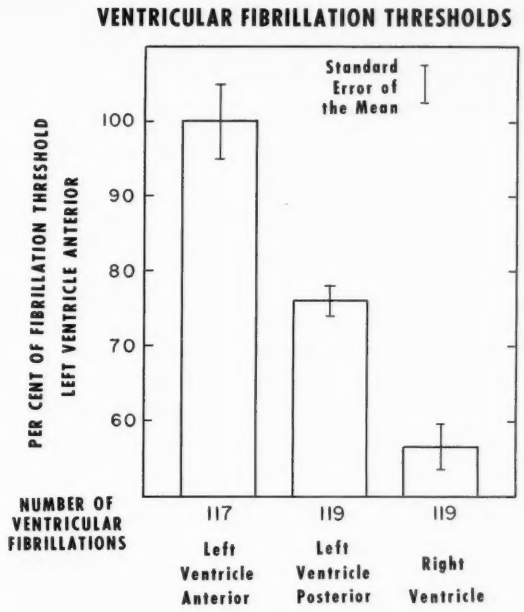
VENTRICULAR FIBRILLATION THRESHOLDS
Standard Error of the Mean
PER CENT OF FIBRILLATION THRESHOLD LEFT VENTRICLE ANTERIOR
100
90
80
70
60
NUMBER OF VENTRICULAR FIBRILLATIONS
117
119
119
Left Ventricle Anterior
Left Ventricle Posterior
Right Ventricle

Fig. 7.

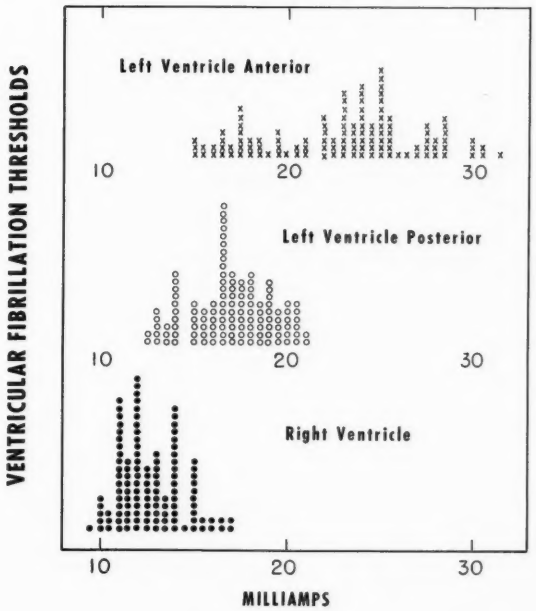
VENTRICULAR FIBRILLATION THRESHOLDS
Left Ventricle Anterior
Left Ventricle Posterior
Right Ventricle
10
20
30
MILLIAMPS

Fig. 8.

demonstrated. The fact that coronary disocclusion is followed promptly by resumption of control thresholds would support a more radical therapeutic program for patients with acute coronary occlusion. A final observation from these data is the rather consistent difference between thresholds determined over the anterior and posterior surfaces of the left ventricle. Ventricular fibrillation thresholds over myocardium supplied by the anterior descending artery were higher than those ascertained by stimulation of the posterior surface of the left ventricle. These findings suggest that ventricular fibrillation thresholds vary in a regular manner with respect to left ventricular anatomy.

ANATOMIC VARIATIONS IN VENTRICULAR FIBRILLATION THRESHOLDS

This group of experiments was devised to test the hypothesis that ventricular fibrillation thresholds were not everywhere the same over the cardiac surface but, in fact, observed a specific pattern. After a few pilot studies in which a large portion of the heart was scanned for differences in fibrillation thresholds, the experimental design was established. Ventricular fibrillation thresholds determined over the right ventricle and the anterior and posterior surfaces of the left ventricle were compared.

Fig. 6 is the electrocardiogram of a typical threshold determination illustrating the effects of increasing the current. Fig. 7 is a graph of the results obtained in 10 dogs with a total of 355 determinations. The probability that any two of the columns are drawn from the same population is less than one chance in 100. Fig. 8 depicts the general distribution of the thresholds, clearly denoting the consistency of pattern.

SUMMARY AND CONCLUSIONS

A method for the determination of ventricular fibrillation thresholds is described in detail. The technique is precise and quantitative. So-called fibrillatory and antifibrillatory states and agents should be subjected to such an analysis.

Ventricular fibrillation thresholds are greatly diminished during coronary occlusion but only over the infarct itself; adjacent, noninfarcted myocardium exhibits no diminution in fibrillation threshold. Release of coronary occlusion is followed promptly by threshold values of control levels even after intermittent occlusion over a period of several hours.

A specific pattern of fibrillation threshold differences seems to exist with respect to ventricular anatomy. The right ventricle is most susceptible to fibrillation, followed by the posterior surface of the left ventricle, then the anterior aspect of the left ventricle.

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(For Discussion, see page 703)

DIRECT SURGICAL PROCEDURES ON THE CORONARY ARTERIES: EXPERIMENTAL STUDIES

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THE treatment of peripheral arteriosclerotic obstructions of the lower extremities has improved greatly through the replacement of indirect surgical techniques by direct surgical treatment. These have been applied during the past 6 years to an ever-widening group of patients. After the initial introduction of practical methods in the aorta, iliac, and femoral regions, subsequent progress has consisted of refinements in the actual techniques used and in the selection of operable lesions.

Similar substitution of direct for indirect methods of treatment in the field of coronary heart disease is to be expected. The added difficulties arising from the small caliber of the vessels involved and the relative inaccessibility of the coronary vessels to roentgen study require and are receiving attention. Radiographic selection of patients whose coronary occlusion is suited to some form of direct surgery has been suggested by the retrograde coronary arteriograms produced by catheterization of the base of the aorta.[1, 2] The rapid sequence exposures by cinefluorography offer even greater promise of accurate localization.

Experimental approach to the technical problems to be encountered has been made by Murray[3] and by Absolon and his associates.[4] The technique of Murray consists of replacement of segments of the coronary system by small grafts. Absolon explored the possibilities of endarterectomy using autopsy hearts and of anastomoses between a systemic artery and a coronary artery in dogs. The group represented by Absolon concluded that endarterectomy in the human heart was feasible and the principle has been applied clinically by Bailey.

The controversy concerning the results of indirect methods of myocardial revascularization in addition to the distinct promise of trials at direct techniques has led us to explore some aspects of the latter.

MATERIAL AND METHODS

The present report concerns connection by direct anastomosis of either the internal mammary artery or a homologous graft from the ascending aorta to the circumflex branch of the left coronary artery. Medium- and large-sized mongrel dogs, 50 to 65 lbs. (hearts 200-220 Gm.), were used to approximate the coronary artery caliber of human adults. Only the largest animals actually approached this size.

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All operations were done under general anesthesia induced and maintained with intraperitoneal barbiturate. A left thoracotomy was used in mammary-coronary anastomosis and a transverse bilateral thoracotomy was used in the graft cases. Respiration was carried on by mechanical insufflation of the lungs with air. In mammary artery transplants, the left internal mammary artery was dissected from the sixth interspace below to its origin above prior to completing the incision. All operations were done under normothermic conditions.

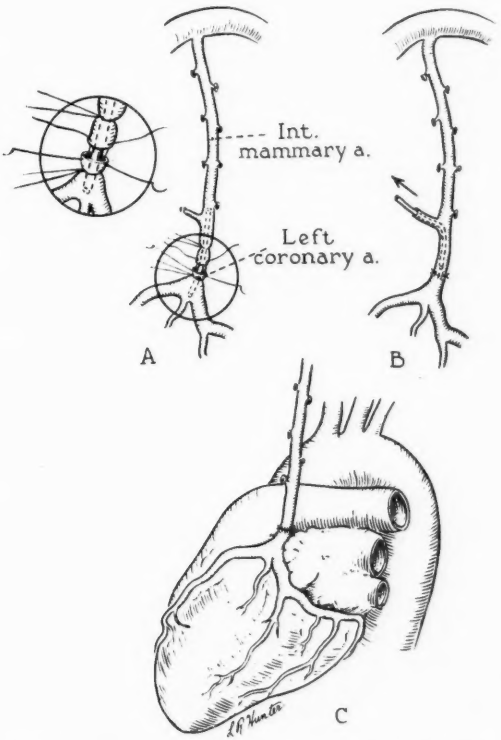

Fig. 1.—End-to-end anastomosis of the left internal mammary artery to the circumflex coronary artery done during normal cardiac action. The coronary circulation is maintained during anastomosis through a small catheter which is removed through a mammary artery branch.

Group A.—Twenty animals prepared in this manner and the left thoracotomy done with the mammary artery freed were subjected to operation during normal cardiac action. The circumflex coronary circulation was continued while the end-to-end mammary coronary anastomosis was being made through a No. 20 polyethylene tube threaded into both vessels. The anastomoses were performed with interrupted technique using No. 5-0 or 6-0 braided silk sutures on atraumatic needles. The sutures were placed as accurately as possible one

millimeter apart and less than one millimeter from the cut edge. For the purpose of training, magnification was not used. At the conclusion of the anastomosis, the inlying tube was removed through a branch of the mammary artery which had been left long for this purpose (Fig. 1). Some of the animals in Group A were kept for later study after surviving the procedure. Others were sacrificed immediately after nonsterile procedures which had been done to develop facility with the anastomosis and dissection. The survivors were studied after periods up to 6, 9, and 12 months to determine patency of the mammary artery and the anastomosis and to observe any ischemic changes in the myocardium of the left ventricle. Arteriograms of the anastomotic system were made.

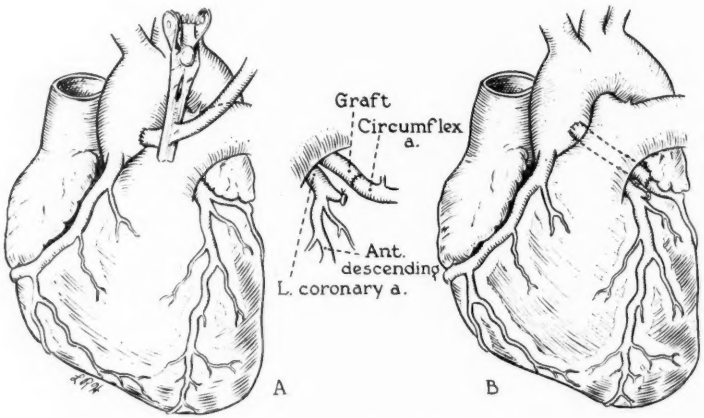

Fig. 2.—Small homologous artery graft implanted between the aorta and the circumflex coronary artery during cardiac arrest and extracorporeal circulation. In this instance, the graft was passed behind the pulmonary artery. An anterior position was produced in other animals.

Group B.—Seven animals were prepared and subjected to the transverse incision without dissection of the mammary artery. The superior and inferior venae cavae and the left subclavian artery were isolated for connection to an extracorporeal pump-oxygenator of the bubble type. The left coronary artery was then dissected from surrounding fat and the anterior descending, septal, and circumflex branches were identified (Fig. 2). A long segment of the circumflex branch was then isolated avoiding damage to the left auricular branch. As the second step in the procedure, a suitable portion of the ascending aorta, 2 to 3 cm. above the aortic valve, was excluded using a curved Potts coarctation clamp. A segment of homologous common or external iliac artery, taken under sterile conditions and stored for a short time in a moist gauze sponge, was then anastomosed end-to-side to the aorta. The end of the anastomosed segment was clamped and the aorta clamp removed to test the connection and allow for clot sealing of small leaks before the animal was heparinized in preparation for extracorporeal circulation. The connections to the pump-oxygenator having been made and heparinization accomplished (2.5 mg./Kg.), cardiac asystole was

induced by cross-clamping the aorta proximal to the graft implantation site and injecting a suitable amount of 25 per cent potassium citrate diluted to 2.5 per cent with heparinized blood. Under cardiac arrest and total body perfusion, the circumflex coronary artery was ligated distal to the auricular branch, transected distal to the ligature, and the cut end prepared for anastomosis. The graft was approximated to the transected end of the coronary artery, sometimes anterior to the pulmonary artery and sometimes behind it. The graft was cut to proper length allowing for the expansion of the pulmonary artery which would occur later. An end-to-end anastomosis was made using the same technique as in Group A but without the need of the polyethylene tube. Air was excluded from the graft before completing the anastomosis. After the preparation was complete, coronary circulation was restored by removing the clamp from the aorta and the smaller clamp from the graft segment. The left ventricle was observed for color changes indicating proper perfusion through the graft and circumflex artery. Survival was not routinely sought in these procedures and the preparation of the pump-oxygenator was not always sterile. Studies were made in the acute experiments by simple observation of myocardial color and maintenance of normal rhythm after the heart had resumed action. After a period of 30 to 180 minutes of observation, incisions in various points along the circumflex distribution were observed for blood flow and an arteriogram was done.

RESULTS

The results, as they pertain to mortality or success of the procedures, are not strictly comparable between Group A and Group B. All twenty of the Group A were completed before Group B was started because of a wish to economize on time by gaining proficiency in the techniques before the more laborious operations with the pump-oxygenator were done (Table I).

TABLE I

METHOD	NO. OF ANIMALS	MORTALITY			SURVIVALS
		OPERATIVE	POSTOPERATIVE		
		VENT. FIB.	THROMBOSIS	HEMORRHAGE	
Group A	20	7	4	0	9
Group B	7	3	0	2	2

Group A.—Of the twenty procedures in this group, nine were successful in producing indefinite survival. In the mortality of 11 animals are represented 7 animals dying during the procedure of ventricular fibrillation and 4 dying in the postoperative period. All 4 of these animals were found at autopsy to have developed thrombotic occlusion of the mammary artery.

Five of the surviving animals have been sacrificed for study, 4 survive for longer periods of observation. In the 5 examined, the mammary artery was found to be widely patent and there was no instance of change in the area of myocardium which was supplied by the transplanted artery. Clamping the mammary artery produced ventricular fibrillation in all 4. Arteriograms showed the unobstructed lumen of the arteries and their anastomoses (Fig. 3).

Fig. 3.—Arteriogram produced immediately after sacrifice of an animal 6 months after left mammary-circumflex coronary anastomosis. The opaque material was injected into the mammary artery near its origin.

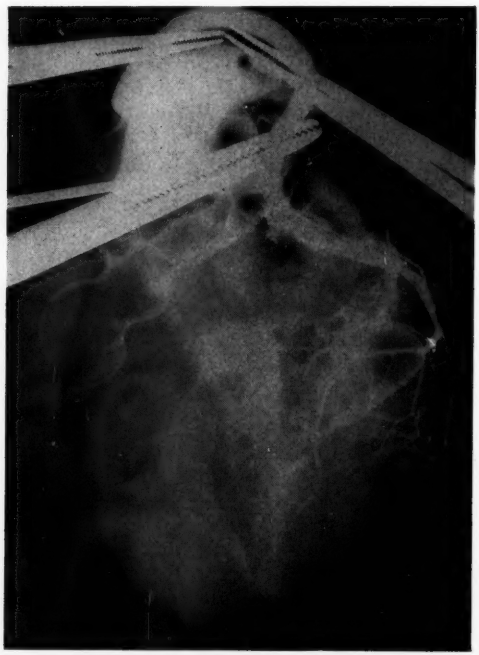

Fig. 4.—Arteriogram of a fresh specimen in acute experiment in which the ascending aorta and the circumflex coronary were connected by a graft. The sweeping curve taken by the graft is caused by its position anterior to the pulmonary artery.

Group B.—Considerably greater ease of anastomosis was experienced with the heart in asystole. This comfortable atmosphere was at the expense of the danger of cardiac arrhythmias during re-establishment of cardiac action and of postoperative hemorrhage. The latter was thought to be due to inadequate neutralization of the heparin. There was a complete absence of thrombotic occlusion of the graft which had occurred in 4 of the 20 animals in Group A.

Of the 7 animals in this group, only 2 survived during the period of observation. There was an operative mortality of 3 due to ventricular fibrillation and an early postoperative mortality of 2 due to hemorrhage from the distal suture line. Since survival was not the particular aim of this series, the immediate success rate dependent upon completion of the preparation and restoration of a stable cardiac action was 4 out of 7.

The advantage of a quiet heart was the only observable benefit accruing from the more elaborate operation. The use of a graft instead of the internal mammary artery avoided the increased resistance of the longer, narrower and more tortuous route supplying the heart through the new connection. The pressure and color of the circumflex system after the anastomosis were more favorable after the use of a graft although it appeared to be quite adequate when the mammary was used (Fig. 4).

DISCUSSION

Very little technical difficulty was encountered in the making of anastomoses to the circumflex coronary artery in spite of its comparative small size. In the larger vessels of average human subjects this aspect would be facilitated. The presence of obliterative arterial disease in a clinical patient can be predicted to add difficulties of undeterminable degree. The ease of suturing was considerably increased by induced cardiac arrest. This was true even though the anastomoses were carried out at the cardiac base where motion of cardiac action is narrower than at the apex. In clinical work the point at which such work would probably be required may often be away from the base and the value of asystole be greater.

Survival and coronary competence were good when the internal mammary artery was used. Some doubt as to the ability of this vessel to supply the coronary system was entertained initially because of a theoretical disadvantage derived from the length of new coronary channel. It was thought that the phase of most efficient flow would be disturbed and that the pulse wave might reach the coronary vessels when the heart was in systole to the detriment of flow.

In the first few attempts utilizing cardiac arrest, greater difficulty was encountered in restoring sinus rhythm after completion of the operation than had been experienced in other, noncoronary, types of experimental procedures. Some delay in washing out of potassium from the left ventricle, due to increased resistance in the artificial circumflex system, was thought to be responsible. However, attention to details of inducing the arrest diminished this trouble. The minimum dose of potassium which, when rapidly injected, brings about asystole produces a more easily reversed arrest than the larger dose usually required

when the rate of administration is slower. If coronary resistance is an important factor in the thoroughness with which the arresting ion is eliminated from the myocardium it could be a very serious clinical feature. In patients with coronary artery disease the resistance could be very high and failure to restore sinus rhythm after arrest might prohibit the use of potassium for this purpose.

Thought must also be given to the long-term behavior of the artificial coronary channel of either type. The fate of a very small caliber arterial homograft is not known. If tissue reaction and infiltration of the vessel produced constriction the result would be serious. The length of the freed internal mammary artery and its unnatural new course from subclavian to coronary artery exposes it to constriction or obstruction and could be a limiting factor to its clinical use. The additional factor of constant motion adds to this theoretical danger.

SUMMARY

Twenty-seven medium- and large-sized dogs have been provided with extracardiac sources of circumflex coronary artery blood supply. In 20, the internal mammary artery was anastomosed to the coronary artery, end-to-end, during normal cardiac action, the circulation being maintained through a small polyethylene tube. In 7, a graft was implanted between the ascending aorta and the circumflex artery during induced asystole and total cardiac bypass.

2. The advantage of cardiac arrest technique is the greater ease of anastomosis in the quiet heart. A disadvantage is an apparently increased difficulty in restoring sinus rhythm after the coronary procedure.

3. Both methods are entirely feasible in clinical coronary artery disease but are dependent on a number of factors which are discussed. Outstanding among these are the problems of exact anatomic diagnosis and of lack of assurance of the long-term fate of a transplanted segment of mammary artery or a small caliber arterial homograft.

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(For Discussion, see page 703)

LIGATION OF THE INTERNAL MAMMARY ARTERIES AS A MEANS OF INCREASING BLOOD SUPPLY TO THE MYOCARDIUM

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CORONARY arterial disease holds the dubious distinction of being the major cause of death and disability in the field of cardiac disorders. Its prevalence seems paradoxically to be increasing despite mounting efforts to modify its ravaging but insidious course. Basically, the offending lesion is that of arteriosclerotic vascular degeneration with its resultant gradual or sudden occlusion of portions of the arterial tree, depriving the myocardium of its only source of sustenance. Although inroads have been made toward the modification of this sclerotic process by metabolic means, the ultimate solution seems remote at the moment. In the interim both physician and surgeon have attempted to improve myocardial vascularity, despite the natural progression of occlusive changes, by augmenting its diminished blood supply from neighboring vascular structures or by redistribution of myocardial blood from unaffected to affected areas.

In this regard the valiant efforts of the many investigators, past and present, need not be reviewed here.[1-6] It is enough to add or enlarge upon but another facet in the array of surgical attempts designed to bolster the flagging myocardium even though ultimately this and all other such methods seem destined only to fight a delaying action until the main offender—sclerosis—can be abolished.

In 1939, at the suggestion of Fieschi[7] in Italy, Zoja and Cesa-Bianchi ligated the internal mammary arteries of a patient who for some years had suffered from repeated myocardial infarcts. The operation was performed under local anesthesia and the patient enjoyed an excellent postoperative course. To quote Fieschi, ". . . the patient, after two years, is still alive and has had no further acute attacks of infarction." This operation was the culmination of Fieschi's rather modest attempts to amplify known anatomic demonstrations of the naturally occurring communications found between the ramifications of the internal mammary arterial bed and the coronary circulation. Previously he had been able to trace, by radiopaque injections, vascular channels from the

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internal mammary artery through its pericardiophrenic branch into a few periaortic and peripulmonary arterial rami. It was his hypothesis that the coronary arterial circulation might be favorably influenced by creating hypertension in the circulatory collateral of the mammary arteries by occluding these vessels in the second intercostal space. Indifference on the part of his professional contemporaries prevented expansion of this effort just as a similar apathy has impeded the enthusiasm of most investigators throughout the world regardless of their field of endeavor.

In 1955, Battezzati, Tagliaferro, and De Marchi[7] amplified the work of Fieschi and reported the results of their anatomico-surgical research both experimental and clinical. In cadavers they injected methylene blue and India ink at the level of the second intercostal space into a segment of the internal mammary artery containing the origin of the pericardiophrenic artery after occlusion of the mammary at the subclavian artery. Excellent mapping of the vascular network within the parietal pericardium was obtained and on occasion the dye could be seen in the vascular rami of the myocardium and epicardial fat. The same but more complete and detailed findings were obtained in dogs.

Eleven patients, suffering from angina pectoris caused by coronary sclerosis, were subjected to internal mammary arterial ligation by them. In each, the anginal syndrome was abolished and remained so even after the patients had returned to normal activity. In addition, the signs of myocardial insufficiency, particularly dyspnea, disappeared in most of those in whom it was present as did the electrocardiographic tracings of myocardial ischemia, and the ballistocardiographic recordings were modified favorably in 8 of the 11. In an addendum, they reported that 14 additional patients had obtained similar clinical and objective improvement.

This highly favorable report stimulated the authors to repeat these studies and to observe at close range the phenomena which had presented itself to the Italian workers. It must be readily admitted that considerable skepticism as to the efficacy of such findings and results was entertained. Even though anatomic channels between the internal mammary and coronary arterial systems existed, it seemed unlikely physiologically that a sufficiently increased vascular flow between the two could be obtained by such means. On the other hand, if such an innocuous procedure, surgically speaking, could result in even a portion of the reported findings then surely a contribution of considerable magnitude was at hand. Further, the realization that for its success this method might call into play and enhance naturally existing channels, which the body itself employs under stress and stimulus, made this investigation doubly attractive.

ANATOMIC BACKGROUND

As early as 1880 Langer[8] pointed out that the vascular system of the heart was not an independent circulation. He observed the vasa propria of the heart (arterial and venous) to anastomose extensively with the vessels of the pericardium, the bronchial vessels, and the diaphragm via the vasa vasorum of the

great cardiac vessels. He stated that these extracardiac coronary anastomoses made it possible to feed the heart collaterally after the obstruction of a main coronary branch.

Gross,[9] in 1921, confirmed this earlier work by showing distinct connections between the coronary arteries and the vessels of the parietal pericardium. He further commented upon the development of the rami telae adipose with advancing age, with or without the stimulus of disease within the coronary arterial pathways.

Woodruff,[10] in 1926, and Wearn,[11] in 1928, noted anastomoses between the finer branches of the coronary arterial tree and the vasa vasorum and other vessels from the ascending aorta. Robertson,[12] in 1930, stressed the importance of the vasculature within the fat pads of the heart as they overlie the major coronaries coursing along the atrioventricular grooves as playing a part in bridging the gap between coronary and systemic vessels within the mediastinum. Many others have confirmed these findings to verify conclusively the existence of extracardiac coronary anastomoses.

In 1932, Hudson, Moritz, and Wearn[13] in a most enlightening study injected the coronary arteries at their ostia with solutions containing India ink, lampblack or 10 per cent bismuth oxychloride under a positive pressure of 220 mm. Hg for 5 minutes or longer with the heart in situ. The extracardiac coronary anastomoses shown in this manner were most extensive and widespread. From the major coronary vessels, communications were shown to the pericardiophrenic branches of the internal mammary arteries and the anterior mediastinal, pericardial, bronchial, superior and inferior phrenic, intercostal and esophageal branches of the aorta. The most extensive anastomoses between the cardiac and extracardiac vessels were around the ostia of the pulmonary veins but also along the root of the aorta, pulmonary artery, venae cavae and wherever the pericardial reflections occurred (Fig. 1). As an extension of the same study Moritz, Hudson, and Orgain[14] reported that in 4 patients the extracardiac coronary anastomoses were increased due to pericardial adhesions. Beck, Tichy, and Moritz[15] employed this knowledge as a basis for the surgical production of pericardial adhesions to augment these extracardiac anastomoses.

EXPERIMENTAL METHODS AND DATA

That there are significant extracardiac anastomoses with the coronary arterial bed is unquestioned. Whether these normal and slowly increasing (advancing age) intercommunications can be used as the pathway for rapidly increasing blood supply to the myocardium and promotion of intercoronary anastomoses remains to be proved. Undoubtedly such proof on a quantitative manner will be difficult if not impossible to obtain for the very nature and diversity of the vascularity involved presents almost insurmountable problems for measurement. Great care must be taken in all experiments to avoid damage to the very vessels one is trying to evaluate.

To verify further the existence of a significant communication between the internal mammary and coronary arterial systems, injection studies were

made in 9 normal dogs. Each dog (average weight, 14 Kg.) was anesthetized with intravenous Nembutal (30 mg./Kg.) and respiration maintained by endotracheal oxygen. The sternum was split vertically and the pericardium opened vertically in the midline in such a manner as to avoid all but the tiniest pericardial vessels. The internal mammary arteries were isolated in the third interspace, incised and cannulated with plastic tubing to the level of the second interspace. In some, the first and second intercostal arteries were ligated, in

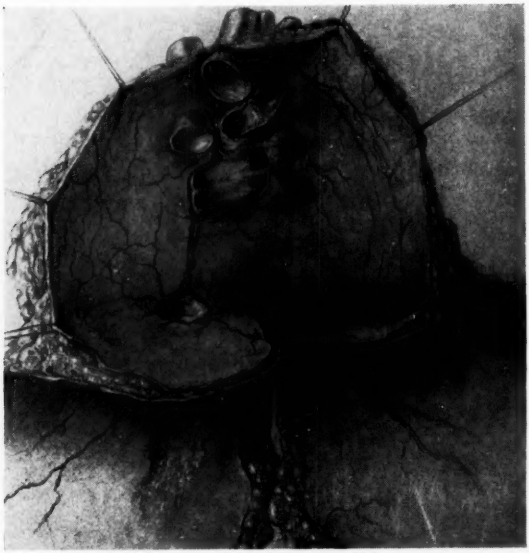

Fig. 1.—The coronary arteries have been injected with the heart in situ. After removal of the heart the extensive extracardiac anastomotic channels originating from the region of the great vessels and pericardial reflections can be seen throughout the parietal pericardium. (From Hudson, Moritz, and Wearn: J. Exper. Med. 56: 919-925, 1932.)

others they were left patent. The two cannulae were connected to a Y tube which emerged from a pressure bottle system containing 3 c.c. of Evans Blue dye (T-1824) and 1 c.c. of 2 per cent fluorescein in 100 c.c. of normal saline solution. Most of the dogs had previously been heparinized. The origins of the internal mammary arteries were ligated at the subclavian arteries. Then, rapidly, the superior and inferior venae cavae and the azygos vein were tightly ligated and the hilus of each lung containing bronchus, pulmonary artery, and veins were clamped. Care was taken not to destroy more than a minimum of vascular anastomotic channels, particularly when ligating the superior vena cava, for the phrenic nerve and pericardiophrenic artery are in close proximity. These occlusion maneuvers, after mobilization of the structures as described, were accomplished in not more than one minute. Ten microcuries of I^{131} were then injected into the tubing from the dye solution container, and the pressure raised to 150 mm. Hg within the injecting system. From 2 to 8 minutes were

consumed for the full amount of solution to disappear into the pericardiophrenic arterial system. At 30-second intervals 1 to 2 c.c. samples were withdrawn from the coronary sinus for analysis. Occasionally samples were also taken from the anterior descending coronary artery. In other instances, either the circumflex artery or the anterior descending artery was divided and the character and nature of its retrograde flow determined. In 2 dogs, a Foley catheter was inserted into the left ventricle at its apex and passed up into the aorta and inflated to block the aorta and coronary ostia from within, thus avoiding disturbance to collateral channels at the root of the aorta (Fig. 2).

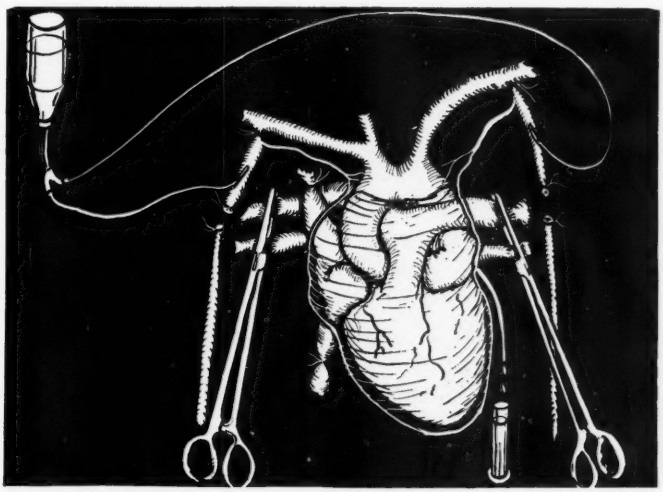

Fig. 2.—Schematic representation of method used to demonstrate communications between the internal mammary and coronary arterial circulations. The internal mammary arteries are ligated at the subclavian arteries, the venae cavae and azygos vein are also ligated and the hilus of each lung (pulmonary artery, vein, and bronchus) clamped. The pericardial attachments are disturbed as little as possible. Repeated samplings from the coronary sinus were taken.

The results of these nine experiments were as follows:

1. Significant quantities of dye were visualized in all animals in the small vessels throughout the parietal pericardium (in the mediastinal pleura and fat), around the base of the aorta and pulmonary artery and venae cavae, in the walls of the atria, in the epicardial fat over the atrioventricular grooves and, repeatedly, in the small plexuses of vessels underlying the epicardium. In one instance, the entire thickness of the left ventricular myocardium was stained with dye even out into the base of the papillary muscles.

2. Gross dye mixed with blood was observed to flow from the distal ends of the transected circumflex or anterior descending artery in those dogs so prepared.

3. Radioactive iodine was found in the venous specimens removed from the coronary sinus in increasing amounts, with the usual peak reached from 5 to 10

minutes after injection. The peak was somewhat variable but for the most part followed a set pattern.

4. One-centimeter segments of left ventricular myocardium and the posterior interventricular septum were routinely found to contain radioactive iodine.

5. The source of this extracardiac arterial supply by the conditions of the experiment could only be by way of the pericardiophrenic artery to the parietal pericardium, thence to the myocardium under the epicardium along the roots of the great vessels and at the reflections of the pericardium.

As a natural corollary to these studies, quantitative measurements of coronary backflow are desirable. As yet these observations have not been made but preparations for such a study in this laboratory are in progress.

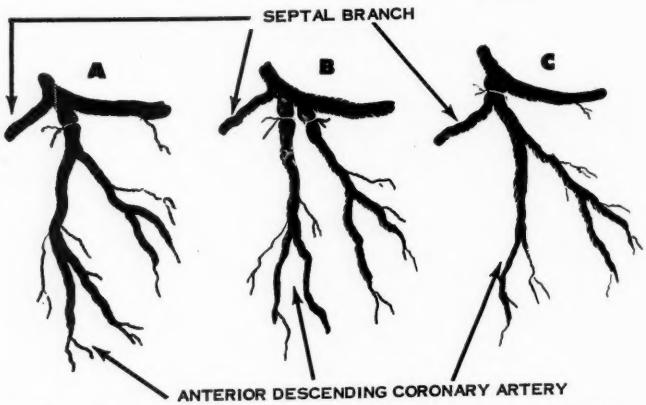

Fig. 3.—Diagram to show left coronary artery and its common variations.

A is its usual pattern and point of ligature in these experiments.

B, The first branch usually arising from the descending coronary shown arising from the circumflex coronary artery requiring a second ligature.

C, Ligation at the origin of the descending coronary artery has inadvertantly included a low lying septal branch (such ligations were excluded from this study).

An attempt has been made to evaluate the degree of protection preliminary ligation of the internal mammary artery may afford the experimental animal when subjected to the production of sudden, acute myocardial infarction by ligation of the anterior descending coronary artery at its origin. The performance of this type of experimentation must likewise be done with great care and due regard for the variations in the anatomy of the left coronary artery observed. The left coronary artery divides, approximately 1 cm. from its origin at the aorta, into the circumflex artery which continues around the heart in the atrioventricular groove and the anterior descending artery coursing down over the anterior aspect of the heart roughly overlying the interventricular septum. At this bifurcation but variably situated, the septal branch arises and courses posteriorly in the interventricular septum. Just beyond the origin of the anterior descending artery, its first branch, which is rather large, swings laterally and downward over the anterolateral aspect of the left ventricle. Thus,

ligation of the anterior descending artery in this experiment is designed to occlude both the anterior descending artery and its first branch as described but the septal branch is spared. Not infrequently the first branch of the anterior descending artery instead of arising from its normal parent artery arose from the first portion of the circumflex artery so that under these circumstances a separate ligature was employed to occlude it at this aberrant origin (Fig. 3). By following this method, close uniformity was maintained throughout the experiment. It was hoped that survival in the control group would approximate 30 per cent so that infarct size could be compared with that of the "protected" group of animals. The "protected" group of dogs were treated in the same manner but in these the internal mammary arteries were ligated immediately before, at 24 hours, and at 48 hours before ligation of the anterior descending coronary.

In 14 control dogs, the anterior descending coronary artery with the aforementioned branch to the anterolateral aspect of the left ventricle was ligated. Nine of these animals went into ventricular fibrillation and died within 5 to 20 minutes. Attempts to resuscitate them by defibrillation and massage were to no avail. Four others died within 24 hours. One dog lived 2 weeks and died in pulmonary edema. Thus, these control animals were judged on the basis of survival rather than upon size of infarction for obvious reasons.

	NO. OF DOGS	DIED AT OPERATION	DIED IN 24 HRS.	SURVIVED 5 DA. OR MORE	LIVING
		Unprotected			
	14	9	4	1 (7%)	0
		Protected by Bilateral Ligation of Internal Mammary Arteries			
5 min. to 45 min. before	4	0	1	3	2
24 hr. before	7	1	2	4	2
48 hr. before	8	3	1	4	3
Total	19	4	4	11 (58%)	7 (36%)

Fig. 4.—Total data obtained in 33 experiments to show a possible measure of protection provided to the myocardial circulation by bilateral internal mammary artery ligation (BIMAL).

In 19 dogs, bilateral ligation of the internal mammary arteries was performed 5 to 45 minutes, 24 hours, and 48 hours before ligation of the anterior descending coronary artery as above. The time interval seemed to make little or no difference in the degree of protection provided. Four of these animals died within a few minutes in ventricular fibrillation and 4 others died within 24 hours. The remaining 11 dogs (58 per cent) lived 5 or more days and 7 (36 per cent) are still living having recovered completely (Fig. 4). Each heart of the 26 dogs who eventually died was carefully dissected and in each the septal branch from the left coronary artery was patent and uninjured. Six dogs in the original series, both among the protected and unprotected groups, were found to have had the septal branch inadvertently ligated with the anterior descending coronary artery, hence they were excluded from this analysis.

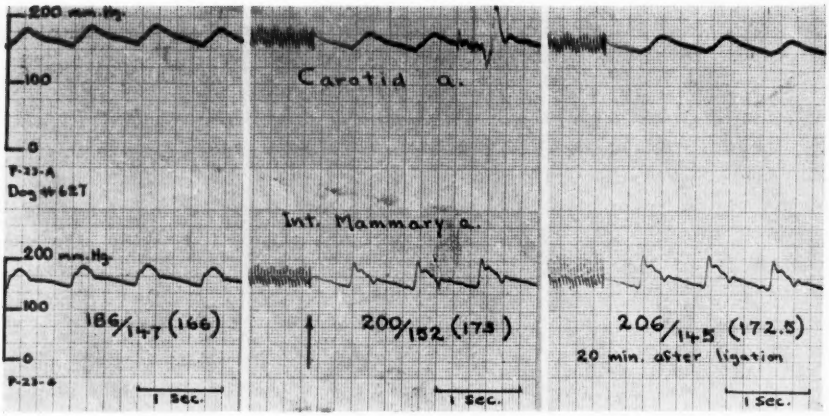

Fig. 5.—Direct pressure tracings taken within the internal mammary artery above the point of ligation at the second interspace. The arrow denotes the moment of ligation. A mean increase of 7 mm. Hg above point of ligature is noted. The upper simultaneous tracing from the carotid artery shows the systemic pressure to remain constant.

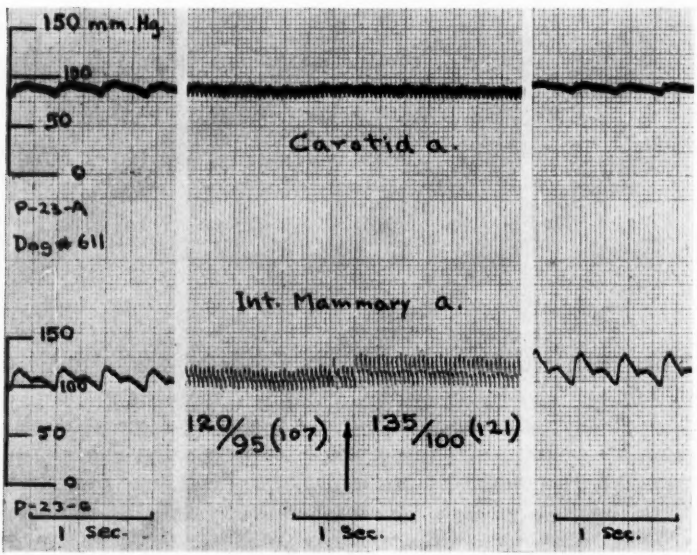

Fig. 6.—Direct pressure tracings taken within the internal mammary artery above the point of ligation at the second interspace. The arrow denotes the moment of ligation. A mean increase of 14 mm. Hg above point of ligation is noted. Tracing on the left taken 30 minutes later.

Under the conditions of this experiment which was closely controlled and meticulously performed it is felt that a significant degree of protection was obtained by bilateral internal mammary ligation in the manner described.

In an intial effort to investigate the hemodynamic pressure changes in the internal mammary artery, above or proximal to the site of ligation, pressure tracings were obtained in 2 animals. In one, a mean pressure rise of 7 mm. Hg (Fig. 5) was noted and in another a mean rise of 14 mm. Hg (Fig. 6) was recorded. Each pressure rise was maintained for 20 to 30 minutes, the full period of observation. Simultaneous measurement of systemic arterial pressure in the left carotid artery showed no pressure variation.

Holman[16] has shown that "the collateral circulation which develops following ligation of a large artery depends upon transforming high 'end pressure' in the parent artery into 'lateral' pressure which, directed into its branches, results in an increased volume flow through them. This increased volume flow distends them and opens up their prearteriolar and arteriolar beds, whence the flow is directed into the prearteriolar beds of the branches distal to ligation,

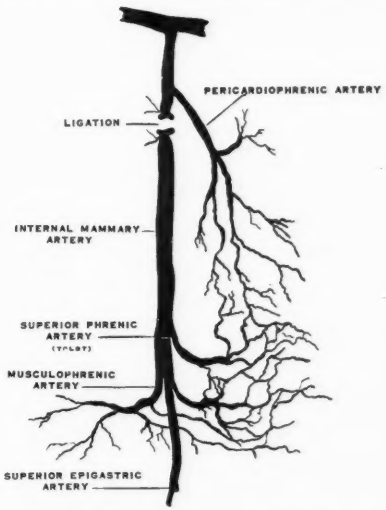

Fig. 7.—Schematic representation of internal mammary arterial collateral circulation as enhanced by ligation at the level of the second intercostal space.

whose low pressure because of the ligation, permits blood to flow through them more readily than through prearteriolar beds elsewhere." This phenomenon would seem to occur in the case of the ligated internal mammary artery where the increased pressure proximal to the ligature is transmitted down the pericardiophrenic artery into the extensive arterial plexus over the parietal pericardium. These vessels freely anastomose with those from the superior phrenic, one of the two arterial terminations of the distal internal mammary artery completing the collateral circuit (Fig. 7). It is believed, and this specific point is presently under investigation in this laboratory, that this circuit is shared by the myocardium through its extracardiac communications with the pericardiophrenic

arterial system and accounts for the clinical improvement in patients so treated. It must be clearly understood, however, that this supposition has not been proved and at present is pure speculation.

CLINICAL APPLICATION

Even as the experimental proof for the efficacy of a procedure of this type is difficult to obtain so also is the evaluation of its clinical application. It has long been recognized that the available clinical methods for objective measurement of the status and severity of coronary artery disease, acute or chronic, are woefully inadequate. Those who have pioneered so magnificently the direct surgical approach to the problem of coronary insufficiency (Beck, Thompson, Vineberg and others) have repeatedly commented upon the fact that the patient's own history and subjective information is far more import in ultimate evaluation than are the electrocardiogram or ballistocardiogram. This has been particularly true when surgical techniques involving pericardiotomy with trauma and the introduction of foreign bodies have been employed. It may be equally true of this technique even though the pericardium and pleura are not entered or disturbed.

Because all advocated techniques to date have required open thoracotomy, erroneously considered by most physicians as highly dangerous in itself, the proper use of myocardial revascularization by these means has never attained its measurable goal. They have rarely been given a chance on a wide scale or over a long period of time. This is perhaps the fault of the surgeon even more than of the physician because of the multiplicity of procedures advocated and their ever-changing modifications. Possibly the introduction of internal mammary ligation as a means of myocardial revascularization, because it is innocuous and easily tolerated even by the desperately crippled patient, may break down the barrier of fear and open the way to a better understandng of what surgery has to offer. At this writing the authors are not laboring under the delusion that the operation herein reported is the "sine qua non" for coronary artery disease and should be used to the exclusion of all others. On the contrary, the Beck I procedure and simple talc poudrage have demonstrated their value and are not to be abandoned or deprecated in the slightest without cause. Bilateral internal mammary artery ligation (BIMAL), to be considered on the same plane as current procedures, has to prove its merit with the passage of time and time alone. It may well be that its proper place will be as an adjunct to existing measures. On the other hand, should it eventuate in clinical results equal to those presently obtained by other means it will surely seek its own level and replace them. In any event it must be tested critically.

Brofman[17] has stated, "The one indication for operation is a positive diagnosis of coronary disease." A more succinct and definite statement could not be made. The patients included in this series were just that. They fall into three categories:

1. Angina pectoris due to coronary insufficiency (arteriosclerosis or hypertensive) primarily past-proved infarction, occasionally without proved antecedent infarction.

2. Arteriosclerotic heart disease with coronary insufficiency resulting in myocardial insufficiency—(a) episodic heart failure, (b) arrhythmias.

3. Hemodynamic coronary insufficiency (angina) due to aortic valvular disease. True coronary artery sclerotic changes may well be absent in this group.

With the inception of any new surgical procedure invariably the clinical material referred for its application represents the last stage of the disease in question—the case in which every other therapeutic measure has failed. The patients in this series were no exception to this time-honored pattern.

Seventy-seven patients have been operated upon to date. The criteria for surgery was the presence of organic coronary insufficiency with agina pectoris as outlined above. No patient with these findings was turned down because of age, debility, unstable disease, frequency and severity of attacks, hypertension, cardiomegaly, past cardiac failure or the like, as has been the case in most series reported and treated by other surgical techniques. In other words they were not carefully culled so that only the better cases were selected. The youngest was 33 and the oldest 82 years of age. Sixteen were over 60 years, of whom 5 were over 70 and 2 over 80. Thirty-nine were male, 11 were female in a series of 50 reported in detail below.

Fifty of these patients have been carefully followed for from one to 5 months and form the basis of this initial analysis. Evaluation of the results obtained has been the sole responsibility of one cardiologist, Dr. J. Roderick Kitchell, Chief of Cardiology at Presbyterian Hospital. Thirty-four (68 per cent) have been clinically improved in that they either have no angina (18 patients, 36 per cent) or now have fewer and less severe attacks of pain (17 patients, 32 per cent). In most of these, improvement or abolition of preoperative pain and discomfort was immediate; in some, 48 to 72 hours were necessary and in a few a week or 10 days elapsed before the eventual result seemed complete. In 11 patients (22 per cent), no clinical improvement is now apparent although several seemed improved for a time. Five patients have died since surgery (Table I). Six of these patients were operated upon within 2 weeks of an acute infarction and 3 of these are now dead (see below). Seven more, making a total of 13, underwent surgery within 6 months of an acute infarction. Much could be added to this brief recitation of figures but in a disease so protean and unpredictable more time must pass before definitive statements should be made.

TABLE I. RESULTS OF BILATERAL LIGATION AND DIVISION OF THE INTERNAL MAMMARY ARTERIES

(50 PATIENTS FOLLOWED 1 TO 5 MONTHS)

	TOTAL GROUP		44 PATIENTS UNDER 70 YEARS	
Improved				
Asymptomatic	18	34 (68%)	18	32 (73%)
Moderate	11		11	
Slight	5		3	
Clinically Unchanged		11 (22%)		9 (20%)
Dead				
Within one month	3	5 (10%)		3 (7%)
Over one month	2			

The underlying pathologic basis for the coronary insufficiency in this group of patients has been summarized in Table II. Although the numbers of cases are far too few to permit conclusions to be drawn, the impression was gained that those with hypertensive cardiovascular disease obtained the better result. Whether the hypertension favored the development of a higher gradient of pressure within the pericardiophrenic arterial collateral bed and therefore greater blood flow is conjectural at this point.

TABLE II. RESULTS ACCORDING TO BASIC PATHOLOGIC PATTERN

	ARTERIOSCLEROSIS		HYPERTENSION		HEMODYNAMIC	
					AORTIC STENOSIS	AORTIC INSUFFICIENCY
Asymptomatic	12	26 (65%)	3	5 (71%)	2	1
Moderate improvement	9		2		0	0
Slight improvement	5		0		0	0
Clinically unchanged	9		2		0	0
Dead	5		0		0	0
Total	40		7		2	1

Of very considerable interest is the correlation of the clinical result obtained in these patients with the type and number of antecedent infarctions sustained. Such an analysis cannot be strictly accurate to the last detail for some overlapping is inevitable. The 45 patients who have been clinically improved or unchanged suffered a total of forty-six infarctions, thus averaging approximately one infarction per patient. The 5 patients who have died averaged more than two infarctions apiece and each of these patients suffered one septal infarction. The inference is that septal infarctions are the more hazardous and the least affected by this procedure (Table III).

TABLE III. CORRELATION OF CLINICAL RESULTS WITH TYPE OF ANTECEDENT INFARCTION

	ANTERIOR		POSTERIOR		SEPTAL		RATIO OF TOTAL INFARCTS
	OLD	RECENT	OLD	RECENT	OLD	RECENT	NO. OF PATIENTS—THIS GROUP
Improved (34 patients)	9	3	13	0	11	1	37:34
Unchanged (11 patients)	2	2	2	0	2	1	9:11
Dead (5 patients)	3	0	3	0	3	2	11:5

Objective Findings.—For some years after the introduction of true cardiac surgery there were many who could not accept the fact that patients were truly improved because of the great discrepancy between functional results and objective proof. No form of cardiac disease has shown itself to be more resistant to exact measurement than has coronary artery disease. This is not the fault of the pathologic entity but rather the inadequacy of professional instrumentation. The patient is certainly not to blame if he feels better, is more productive in society, and is enjoying improved health to the consternation of the physician who just will not believe it because the improvement cannot be documented electrically. Wherein lies the answer?

Thirteen of these patients had electrocardiographic evidence of improvement and 9 had improved ballistocardiograms. Curiously, only one showed improvement in both the ECG and the BCG. Thus, 21 patients (42 per cent) have shown objective improvement compared to 68 per cent showing clinical improvement. This comparison may not be entirely accurate for in only 20 patients have the ballistocardiograms been taken over a month from the time of surgery. Since the ballistocardiographic tracing most frequently deteriorates after any operative procedure during the first postoperative week and these patients were routinely discharged one week after surgery the ballistocardiographic data in over one half of the patients (taken on the sixth postoperative day) may well be altered (Figs. 8 and 9).

Of the 13 (26 per cent) who had improved electrocardiographic tracings after surgery the following changes were observed:

In 10 the depressed ST segments returned toward normal (see Figs. 8 and 9).

Nine had more normal T waves.

Two had improvements in rhythm (Figs. 10 and 11).

One had a definite improvement in voltage.

In one the QRS was less slurred.

Paradoxically, 2 patients who were unimproved clinically had improvement in their electrocardiograms and 2 patients who died of causes other than cardiac had brief improvement in their tracings.

Exercise tests of benefit were not employed in this series for the preoperative diagnosis was not in question in any instance. It was felt unwise to risk the possible complication which occasionally follows such procedures in the more precarious stages of this disease.

Cause of Death.—In only one of the 5 fatalities which occurred after surgery could there be any indictment of the surgery itself. This patient, a 54-year-old white man, had suffered three posterior and one septal infarction. For some hours prior to surgery anginal pain had been all but constant. The administration of Neosynephrin was necessary to obtain a blood pressure reading in the operating room. During the operation, ventricular tachycardia was continuous (all cases are monitored by oscilloscopic and electrocardiographic recordings). In the recovery room the heartbeat deteriorated and stopped and resuscitation was unsuccessful. The operation was obviously ill advised but there seemed to be nothing to lose and everything to gain by the attempt. An autopsy revealed several small infarctions, posterior and septal, but no large single area of necrosis. All coronary arteries showed advanced atherosclerosis. The right coronary artery was completely occluded, one centimeter from its origin.

A second patient, white, male, aged 53, with two healed infarctions, had suffered (noted in retrospect only, as all the electrocardiograms had not been available) another septal extension 18 days preoperatively. He was allowed out of bed on the day of surgery and increased his activities on the next 2 days.

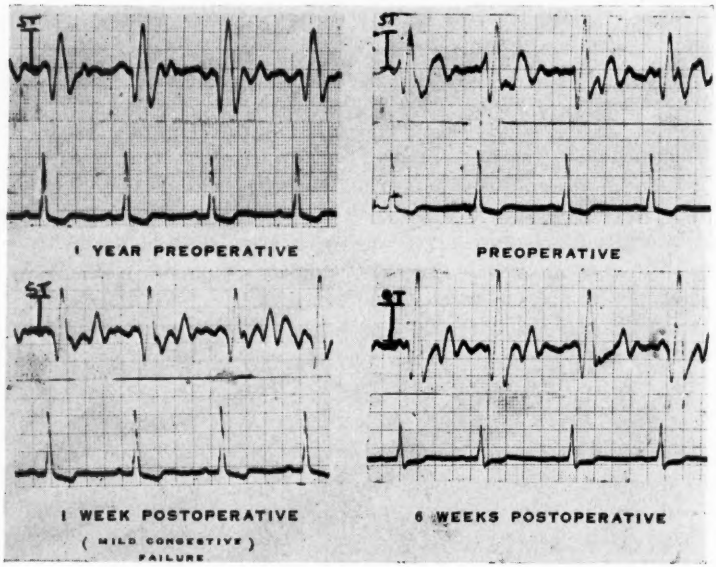

Fig. 8.—Patient J. G., aged 52, syphilitic aortic insufficiency, 4 years' duration severe angina. BCG and ECG tracings taken one year and 2 days before BIMAL (upper tracings) and one week and 6 weeks postoperative (lower tracings). Note the deterioration in BCG during the preoperative year, the fact that no essential improvement has occurred within the first postoperative week. In the 6-week postoperative record note the considerably increased amplitude of the J waves concomitant with her marked clinical improvement.

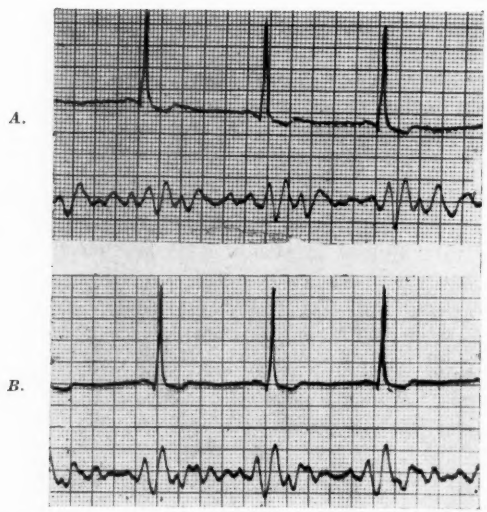

Fig. 9.—BCG tracings made preoperatively (*A*) and one month postoperatively (*B*) in a patient (J. C.) who obtained a marked improvement clinically. In the preoperative record the abnormal H wave has nearly the same amplitude as the J wave. The postoperative record is practically normal with generalized improvement in amplitude.

He collapsed and died suddenly on the third postoperative day. Had the recent infarction been suspected he would have been immobilized for several weeks.

The third patient, white, male, aged 65, with two previous infarctions, did exceptionally well clinically and was discharged on the sixth postoperative day. An ECG taken on the day of discharge was not read until the following week. He remained pain free and active despite an unappreciated small anterior subendocardial infarct which appeared on the final ECG. He died in his sleep on the ninth postoperative day.

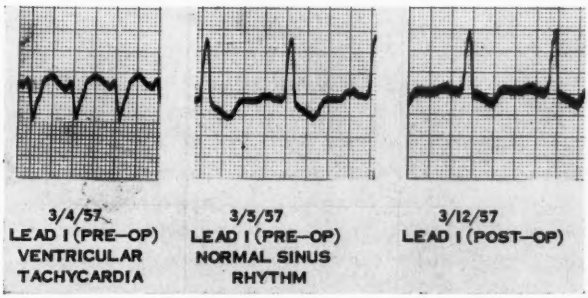

Fig. 10.—ECG tracings in a patient subject to frequent attacks of ventricular tachycardia requiring intravenous pronestyl. There has been only one mild attack postoperatively. Note the shift in axis in Lead I in transition from ventricular tachycardia to the patient's usual left bundle branch block.

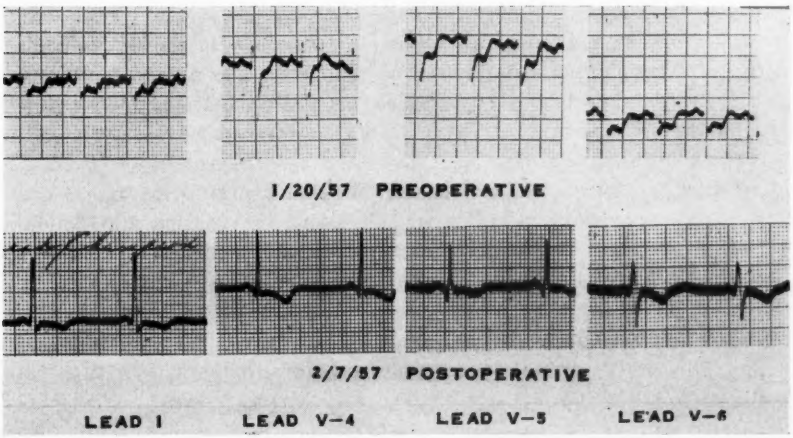

Fig. 11.—Postoperatively, the lessened ST segment depression in all leads shown is evidence of improvement in coronary insufficiency in a patient (Mrs. S. C.) who obtained a marked clinical improvement.

Two other patients, elderly white women, aged 72 and 82, respectively, and suffering from a multiplicity of diseases in addition to old anterior and septal infarctions, died 35 and 31 days after mammary ligation from pyelonephritis, adrenal insufficiency, and congestive heart failure with cardiomegaly

in one and generalized lymphosarcoma in the other. Both obtained marked initial relief of angina and myocardial insufficiency until the terminal stages.

SURGICAL TECHNIQUE

The performance of bilateral division of the internal mammary arteries as compared to other surgical procedures for cardiac disease is safe, simple, and innocuous in capable hands. Although the technical risk is negligible, one must remember that the disease being treated is highly lethal. The application of this procedure and any other will inevitably be followed by the morbidity and mortality of severe coronary artery disease for such operations are palliative not curative.

The choice and conduct of anesthesia are of paramount importance. Two types have been used. For those whose condition is precarious and unstable a local anesthetic, 0.5 per cent procaine, is used. One side is injected and operated completely and then the other. This avoids the sudden introduction of too much anesthetic agent which may tend to lower the blood pressure. No more than 50 c.c. of solution total is necessary when used properly. Those patients who are in good condition and in whom the disease is reasonably stable easily tolerate a light general anesthesia of Pentothal sodium induction and maintenance on 50 per cent N_2O and O_2. Small amounts of succinyl choline may be used as a supplement. Endotracheal intubation is not necessary but should be available.

Bilateral hockey stick incisions are made at the lateral borders of the sternum in the second interspace. Simple transverse incisions are adequate but provide very limited exposure when the interspace is narrow and the musculature well developed. The curved incisions with its reflected flap exposes the entire interspace without restriction. The pectoralis muscle is split and retracted in a normal line of cleavage. The intercostal muscles are incised midway and parallel to the ribs. The fat overlying the pleura is encountered as it surrounds the mammary vessels commonly lying one fingerbreadth lateral to the sternal margin. The vein courses immediately medial to the artery and is left intact. Great care and patience must be exercised when mobilizing the artery from its areolar attachments to the pleura. The artery is divided between ligatures. The right internal mammary artery is commonly larger than the left.

The procedure may be considerably more difficult than it sounds in heavy-set, thick-muscled males. Hemorrhage and inadvertent opening of the pleura can be the only complications and usually are readily controlled. Significant changes in blood pressure must be avoided. Oscillographic and electrocardiographic monitoring is desirable but not essential.

SUMMARY AND CONCLUSIONS

1. A critical although purely preliminary attempt has been made to assess the value of bilateral ligation and division of the internal mammary arteries as

a means of increasing blood supply to the myocardium. The concept for this approach is that of Fieschi. Battezzati, Tagliaferro, and De Marchi have been responsible for reintroducing and amplifying this original concept. The studies reported in this discussion confirm the findings of these Italian investigators. At the moment, however, considerable reservation as to the ultimate place of this surgical procedure is warranted. Whether it will eventually remain as a surgical entity on its own merits or will be used as an adjunct to other surgical techniques cannot be decided until much more investigative work, both experimental and clinical, has been carried out.

2. That there is a naturally developing extracardiac communication between the coronary arterial and pericardiophrenic arterial vasculature has again been confirmed.

3. As yet there is no experimental proof that ligation of the internal mammary arteries bilaterally at the level of the second interspace actually increases blood flow to the heart although the supposition that it does is strongly entertained.

4. There is the decided suggestion that, in dogs, ligation of the internal mammary arteries provides a measure of myocardial protection to the subsequent production of acute coronary occlusion by ligation of the anterior descending coronary artery at its origin.

5. Ligation of the internal mammary arteries at the second interspace is followed by an increase in mean arterial end pressure above the point of ligature in dogs.

6. Seventy-seven patients suffering from arteriosclerotic and hypertensive cardiovascular disease with organic coronary insufficiency and angina pectoris have been subjected to bilateral internal mammary artery ligation (BIMAL). The angina pectoris in 3 of these patients was secondary to advanced aortic valve disease. Fifty of these patients have been carefully followed for 1 to 5 months. By conservative clinical evaluation 34 or 68 per cent of these patients have either lost their symptoms of pain (18 or 36 per cent) or have been immeasurably relieved of their discomfort (17 or 32 per cent). The remainder were unimproved.

7. Objective evidence of clinical improvement lags well behind the observed clinical improvement. In 13 (26 per cent), the electrocardiographic tracings taken one month or more after surgery show obvious improvement and the same may be said in 9 (18 per cent) of the ballistocardiographic studies obtained. As this evidence of improvement occurred on only one occasion in the same patient, objective signs for the better have occurred in 22 (42 per cent) patients.

8. A simple technique for the performance of division of the internal mammary arteries has been detailed.

We are indebted to and acknowledge the very considerable help rendered by Dr. Isaac Starr, Hartzell Research Professor of Therapeutics, University of Pennsylvania Medical School, who supervised and read all ballistocardiograms.

ADDENDUM

Fifty-eight additional patients (135 in toto) of the same type as herein reported have undergone BIMAL. The clinical and objective response has followed the same pattern as described above.

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(For Discussion, see page 703)

THE GRADUAL CLOSURE OF INTERATRIAL DEFECTS

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INTRODUCTION

MOST interatrial septal defects can be closed surgically with few complications and with excellent long-term results.[1-4] However, there remains one group of patients—those having long-standing atrial defects with an associated pulmonary hypertension, pulmonary vascular disease, and a right-to-left shunt through the atrial defect—in which conventional methods of closure have resulted in a high mortality due to right heart failure.[4-7] We have felt that if atrial defects could be closed *gradually* it might be possible for the heart and lungs to adjust to the changes in blood flow.

METHOD

Large interatrial septal defects were created in mongrel dogs (Fig. 1). Most of these animals weighed 40 to 70 pounds, and nearly the entire interatrial septum was excised, leaving a defect 2 to 3 cm. in diameter. At the same operation, a large Ivalon patch was sewn to the edges of the defect. The Ivalon patches contained one or more holes of varying size (Fig. 2). In some of the animals approximately one fourth to one third of the tricuspid valve was excised at the same time, in an attempt to elevate the pressure in the right atrium. Some of the animals also had previously undergone surgery for the production of pulmonary stenosis.[8, 9] In 5 animals, the atrial defect was not repaired with an Ivalon patch at the initial operation. This group underwent repair with perforated Ivalon patches at a later date, when the edges of the defect were endothelialized.

Most dogs were operated upon under hypothermia, and the longer procedures were carried out with the heart in potassium citrate-induced arrest. The heart was restarted in these instances with coronary perfusion of fresh heparinized blood containing added calcium.[10, 11] At variable periods following surgery, the animals were sacrificed and the heart examined and photographed to determine the degree of closure present at that time.

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RESULTS

It was found that smaller defects (3 and 5 mm. in diameter) in the Ivalon patch closed within one week. However, when an interatrial defect was partially closed with an Ivalon patch containing a single hole 8.1 mm. in diameter, gradual closure of this hole occurred over a period of 7 to 30 days following surgery (Fig. 3). In all animals sacrificed during the first week following

Fig. 1.—Heart from dog sacrificed 92 days after the creation of a large interatrial defect. The edges of the defect are endothelialized, and the defect does not show any tendency to close spontaneously.

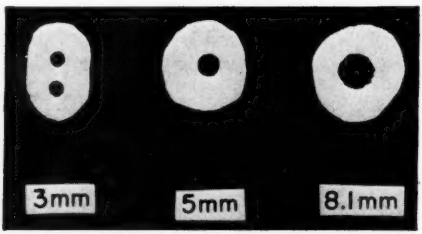

Fig. 2.—Polyvinyl sponge (Ivalon) patches used to repair interatrial defects. Smaller perforations (3 mm. and 5 mm.) usually closed within the first week. When interatrial defects were repaired with Ivalon patches containing an 8.1 mm. perforation, it was found that the perforation remained widely open for one week, but that complete closure occurred after 7 to 30 days.

surgery, the defect in the Ivalon was widely open (Fig. 4). In the dogs sacrificed from 7 to 30 days post surgery, the defect was partially or completely closed, and in all dogs sacrificed after 30 days, the defect was completely closed (Figs. 5 and 6).

The interatrial septal defects in 10 control dogs examined 39 to 145 days after surgery were open in all but one (Table I). The control dog whose interatrial defect closed spontaneously, was the first dog operated upon (in this experiment) by the surgeon concerned, and it was noted at the time of surgery that the defect that was created was rather small.

TABLE I. CONTROL DOGS
(SACRIFICED 39 TO 145 DAYS AFTER SURGERY)

NUMBER OPERATED	NUMBER OF PATENT INTERATRIAL DEFECTS	NUMBER IN WHICH DEFECT HAD CLOSED
10	9	1

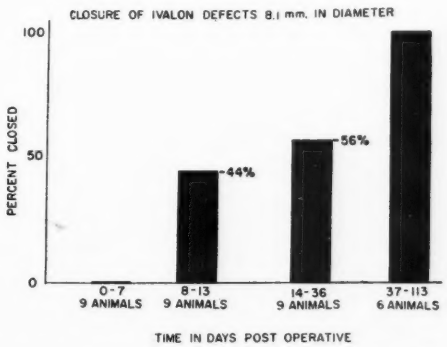

Fig. 3.—This bar graph represents the percentage of dogs showing *complete closure* of the interatrial defect at various time intervals. All animals examined more than 30 days after surgery had complete closure of their IA defect whereas all those examined within 7 days of surgery were widely open.

Fig. 4.—Heart from dog sacrificed 6 days after repair of atrial defect with an Ivalon patch containing an 8.1 mm. perforation. The perforation is only slightly closed.

COMMENT

An Ivalon patch in the interatrial septum is first covered and invaded by fibrin. This is gradually replaced by fibrous tissue, and the defect is then bridged by strands of fibrin and connective tissue. After 30 days the defect is filled in with fibrous tissue, and eventually endothelium covers the entire area (see Fig. 6).

Fig. 5.—Heart from dog sacrificed 10 days after repair of atrial defect with a perforated Ivalon patch. The defect in the Ivalon has been bridged by fibrin and is over one half closed.

Fig. 6.—Heart from dog sacrificed 36 days after repair of IA defect with perforated Ivalon patch. Fibrous tissue has filled in the defect and constricted the Ivalon "doughnut." The entire area is covered with endothelium.

This process of gradual closure is probably due in part to cicatrization of the fibrous tissue invading the Ivalon. We have noted in many of the dogs examined more than 30 days after surgery that the defect in the Ivalon was not only closed, by fibrin or fibrous tissue, but also that the defect in the Ivalon was constricted from its original diameter of 8.1 mm. down to 2 to 3 mm.

In replacing the thoracic inferior vena cava with an Ivalon graft we have observed that gradual contracture of the graft from fibrous tissue in and

around the polyvinyl sponge (Ivalon) results in gradual closure of the graft (Figs. 7 and 8). In the case of Ivalon grafts of the vena cava, this process may take several months, but eventually the graft is completely closed.[12] Although this phenomenon has handicapped our efforts to use polyvinyl sponge for venous grafts, we believe it may prove advantageous when using perforated Ivalon patches to produce gradual closure of interatrial septal defects.

Five animals also had pulmonary stenosis and tricuspid insufficiency. Repair of the interatrial defect in these animals, with a perforated Ivalon patch,

Fig. 7.

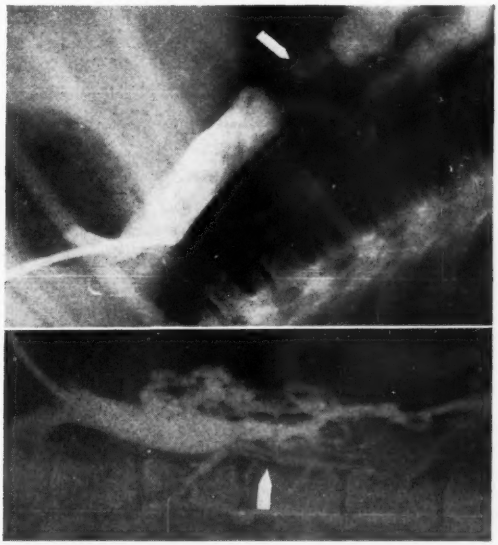

Fig. 8.

Fig. 7.—Venogram 49 days after placement of Ivalon graft in thoracic inferior vena cava (an arrow points to the graft). The graft has been constricted but is still patent. Subsequent venogram showed more constriction. When dog was sacrificed, at 11 months after surgery, the graft was only 3 to 4 mm. in diameter.

Fig. 8.—Venogram 80 days after placement of Ivalon graft in thoracic I.V.C. (an arrow points to the area of the graft.) The graft has been completely closed (verified by sacrificing animal) by constricting fibrous tissue. An extensive collateral circulation has developed.

resulted in a somewhat more gradual closure of the defect than in the other dogs in the series. This observation has little significance because of the small number of experiments. However, we believe that closure of the defect will probably occur over a longer period of time in animals having a markedly elevated right atrial pressure and right-to-left shunt.

Whether or not this method of closing interatrial defects will result in a reversal of the associated pulmonary vascular disease is difficult to say. It has been well established that the pulmonary vascular disease associated with mitral stenosis can be reversed by mitral commissurotomy.[13, 15] Pulmonary vascular disease has been produced in the dog by increasing the blood flow through a lung segment. Resolution of these lesions has been observed, over a period of months, when the blood flow is restored to normal.[16] This evidence supports

the idea that the pulmonary vascular disease associated with atrial septal defects may be gradually reversed by removing the abnormal flow of blood which produced it. Whether resolution of such vascular lesions will occur with the gradual closure of the atrial septal defect awaits further study.

SUMMARY

1. Those patients having interatrial septal defects with associated pulmonary vascular disease and a right-to-left shunt cannot be successfully treated by present-day methods. Sudden closure of the interatrial defect results in right heart failure and death. We believe this group of patients might be cured if their interatrial defects could be closed gradually.

2. Large interatrial defects (3 to 4 cm. in diameter) remained open in 9 of 10 control dogs. These interatrial defects and other similar defects, partially closed with a doughnut-shaped Ivalon patch in which the defect (in the Ivalon) was 8.1 mm. in diameter, all closed in from 7 to 30 days after surgery. The mechanism of closure appears to be gradual bridging and filling of the defect with fibrin and fibrous tissue, and gradual constriction of the doughnut-shaped patch by fibrous tissue invading the Ivalon.

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(For Discussion, see page 703)

PHYSIOLOGIC CONSIDERATIONS OF INTRACARDIAC PRESSURES FOLLOWING CLOSURE OF ATRIAL SEPTAL DEFECTS

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THAT the principal hemodynamic disturbance in patients with atrial septal defect is a left-to-right shunt through the defect is well recognized, but the cause of this shunt has been less clear. In some of our first experiences with closure of atrial defects a prominent thrill was felt as the defect was nearly but not completely closed, and a striking rise in left atrial pressure was noted. As a consequence of this, we have obtained left and right atrial pressures before and after closure of the atrial defect in a number of instances. We wish to present these data with a consideration of the pathogenesis of the left-to-right shunt through the defect and of its surgical significance.

METHOD

Sufficient data for analysis have been obtained on 21 patients undergoing closure of atrial septal defect. Several patients with total anomaly of the pulmonary venous return have been excluded. Those with drainage of the right pulmonary veins into the right atrium were included if repair was modified only by bringing the septum farther to the right in repair than is done in the uncomplicated atrial septal defect. The technique of closure apparently influenced the data little and includes the use of the Gross well,[1] the Sondergaard dissection in the interatrial groove[2] with either interrupted sutures in this groove to grasp the edge of the septum or the purse-string suture described by Björk and Crafoord,[3] and suture under direct vision during circulatory occlusion with hypothermia.[4] Pressures were measured through a 20-gauge thin-wall needle by direct puncture of the various chambers. The needle was connected through a No. 6 cardiac catheter to a Statham strain gauge, and pressure was recorded on a direct writing Sanborn pressure recording system. When care was taken to eliminate all bubbles from the system, satisfactorily undamped pressures were obtained to allow good tracings. Base line pressure was taken with the needle adjacent to the middle of the right atrium. Records of these pressures were reviewed and, in most instances, the mean pressure has been estimated with the use of a compensating planimeter; in a few cases insufficient length of the original tracing has been preserved and only the maximal and minimal pressures are available. Pressures were measured at operation with the thorax open, both before repair of the defect and just before the chest was closed after completion of the repair.

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TABLE I

CASE	AGE	CARDIAC CATHETERIZATION		INTRACARDIAC PRESSURES (MAX./MIN.) MEAN, MM. HG.					
		PULM. FLOW (L./MIN./M.²)	PULM. RESIST. (MM. HG./L./MIN./M.²)	LEFT ATRIUM		RIGHT ATRIUM		PULMONARY ARTERY	
				BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1. S. Mcl.		3.7	8.4	10/7, 8	8/5, 6	5/0, 5	5/3, 5	73/45, 64	85/55, 6
2. E. R.	39	4.6	11.5	12/5	10/5	10/5	8/4	70/40	70/40
3. E. W.	38	5.5	11.2	6/2	5/2	5/0	-	60/25	80/25
4. M. S.	36	34.0	0.84	8/3, 7	17/8, 10	7/5, 6	7/4, 6	45/20, 31	42/20, 31
5. N. M.	11	12.5	1.39	15/5	25/12	5/5	8/5	75/20	45/20
6. H. W.	9	13.4	-	13/9, 11	30/20, 28	13/8, 11	17/10, 14	27/19, 24	30/25, 26
7. R. S.	27	19.3	0.41	7	9	5	7	17	14
8. M. A.	31	9.6	3.52	7/2, 5	10/5, 7	6/2, 4	4/0, 2	50/20, 30	32/20, 23
9. W. V.	6	16.9	0.89	16/5, 12	27/10, 18	13/8, 11	14/1, 9	47/20, 31	38/20, 27
10. O. C.	46	10.4	0.67	11/1, 8	10/3, 6	11/1, 8	5/0, 2	25/12, 22	22/11, 13
11. H. W.	34	High	Low	11/5, 8	22/16, 19	13/6, 11	8/6, 7	26/18, 21	28/16, 21
12. M. L.	45	9.2	2.06	14/4, 9	8/2, 5	11/2, 5	4/0, 3	44/14	
13. F. C.	6	9.6	3.00	17/5, 11	32/10, 17	17/5, 9	12/3, 6	33/12, 21	44/22, 33
14. D. H.	43	-	-	16/8, 10	25/10, 17	15/0, 10	17/4, 8	42/23, 29	35/20, 24
15. M. R.	21	15.0	1.4	8/0, 4	13/3, 10	8/0, 4	6/1, 3	28/10, 17	35/20, 27
16. S. H.	13	High	Low	6/0, 3	9/2, 6	6/0, 3	3/0, 0	38/6, 19	27/7, 12
17. F. N.	5	7.5	1.6	9/4, 6	32/16, 22	9/4, 6	10/5, 7	16/8, 11	32/21, 23
18. J. R.	23	16.9	0.47	11/5, 7	22/7, 18	11/3, 5	8/3, 5	38/20, 26	38/18, 26
19. E. B.	8	12.0	0.33	9/5, 7	26/18, 22	9/5, 7	19/14, 17	27/17, 26	30/20, 24
20. C. G.	5	High	Low	3/0, 2	21/18, 14	3/0, 2	10/0, 5		
21. A. T.	30	15.0	0.66	8/0, 3	9/0, 6	8/0, 3	1		
Average	24	12.5	3.00	7.1	13.3	6.9	5.9	26.6	25.6

Pulmonary flows recorded as high when arteriovenous difference of oxygen was tiny or reversed, making calculated flow inestimably high, pulmonary resistance inestimably low.

Averages based on cases exclusive of those with incomplete data.

Preoperative study of these patients included cardiac catheterization which demonstrated the atrial shunt in all instances. From data thus obtained, pulmonary and systemic flows have been estimated by the Fick principle. In many instances, particularly in young children, the oxygen consumption has not been measured but rather has been estimated as 135 ml. per minute per square meter of surface area. In this laboratory this has been the average oxygen consumption per square meter of surface area, and it is considered that this figure represents as nearly the oxygen consumption at the time of blood sampling, while the child is quiet during fluoroscopy, as measurement from a collection of expired air obtained from a young patient, often anxious concerning the collection of gas. In essence, this means that flows and shunts are estimated on the basis of the arteriovenous oxygen difference and referred to the surface area, the oxygen consumption being considered constant in respect to surface area. An estimate of pulmonary resistance was obtained from cardiac catheterization by dividing the gradient between mean pulmonary artery pressure and left atrial pressure in mm. Hg by the estimated pulmonary flow in liters per minute. In preoperative studies, unless actually measured, mean left atrial pressure was assumed equal to mean right atrial pressure.[5] Normal pulmonary resistance ranges between 1 and 5 mm. Hg per liter per minute per square meter of surface area. (This figure can be readily converted to dynes cm.$^{-5}$/M^2 by multiplying by 60 $\times$ 1.332, or approximately 80.)

RESULTS

Intracardiac pressures taken during operation and before and after repair of the auricular defect are listed in Table I, along with pulmonary blood flow and resistance determined by preoperative cardiac catheterization. Considerable variation of pressures is evident and is not surprising in view of the known changes which occur during operation with the administration and loss of blood, depth and type of anesthesia, and ventilation. Three patients have been listed first in whom the pulmonary artery pressure was high, the pulmonary flow low, and it was felt that the pulmonary hypertension was probably fixed; changes in pressures were least striking in these 3 patients. In all but 2 of the remaining 18 patients the left atrial pressure rose following repair of the defect, as might be expected in view of the normal condition. The tendency was for right atrial and pulmonary artery pressure to fall. A slight rise of left atrial pressure to 5 to 10 mm. Hg was not alarming but, of the 18 patients, 8 had a mean left atrial pressure of more than 15 mm. Hg, ranging up to 28 mm. Hg. Because this striking increase was noted in early cases, we have kept the blood replacement during operation at a less complete level, usually simply matching the suction drainage and excluding the loss of blood on the drapes and sponges. It is probable that if replacement more nearly matched the actual blood loss, left atrial pressures would be recorded higher. In several individuals, and perhaps most strikingly in Patient O. C., a thrill could be felt as the purse-string suture was constricted about the atrial defect. Without further constriction but after inadvertent loss of a moderate amount of blood the thrill disappeared and was not subsequently felt.

The change in left atrial pressure is at the present time unpredictable, as there was no significant correlation with the volume of the pulmonary or systemic flow, vascular resistance, ratio of systemic to pulmonary resistance, or the level of the atrial pressure preoperatively.

All but 2 of these patients are now alive and improved. Patient M. S. developed a supraventricular tachycardia which was present intermittently but frequently for approximately a year but was finally reverted with quinidine; she died the night the rhythm was reverted, apparently of an arrhythmia. The other was Patient J. R. who was felt at operation to have a large insufficient jet through the mitral valve. She developed cardiac asthma on the third postoperative day for about 24 hours and subsequently developed progressive chronic passive congestion. At autopsy, the defect had partially reopened, and there was an old rupture of several of the chordae tendineae with slight prolapse of the mitral valve into the atrium. It was considered that the mitral insufficiency became intolerable when the septal defect, which had served to relieve left atrial pressure, was closed. This may have been one of the relatively minor lesions which impose an insuperable burden on the left ventricle of patients with atrial septal defect as described by Dexter.[5]

DISCUSSION

There is ample evidence that the principal hemodynamic disturbance in patients with auricular septal defect is the increased pulmonary blood flow resulting from a left-to-right shunt through the defect. Several groups have demonstrated, by cardiac catheterization, a slightly higher pressure in the left auricle than the right auricle in patients both with and without an auricular septal defect.[5-9] Little[10] demonstrated, experimentally, a greater pressure rise per unit increase in volume of the left atrium of the dog as compared with the right and cited the observation at human autopsy that the left auricle normally is slightly thicker than the right and presumably has a greater pressure-volume coefficient. Opdyke and Brecher[11] measured pressures continuously in the two atria of dogs and demonstrated a slightly higher pressure in the left atrium during various periods of the cardiac respiratory cycle. This gradient was less in dogs with a surgically created interatrial septal defect.[12] Physical laws of fluid dynamics indicate and measurements confirm,[5] however, that in the presence of a sizable atrial defect no pressure gradient exists. Uhley[13] postulated that the shunt occurs because of a positional difference, the right atrium being below the left atrium in the upright position. The absence of a significant change in the shunt with change of position makes acceptance of this explanation unwise.

Barger, Edwards, Parker, and Dry,[14] and Hull[15] suggested that the shunt is due to relative resistance to filling of the right and left ventricles. Dow and Maloney[16] amplified these observations following studies in dogs with experimentally created auricular septal defects, in which they could demonstrate no measureable difference in pressure between the right and left atria. Dow and Dexter[5, 17] investigated this concept in patients with atrial septal defects and

correlated ventricular output with atrial pressure. With elevated atrial pressure, output of the right ventricle increased while that of the left decreased, and the common atrial pressure appeared to depend more on left than on right ventricular function.

Our concept of the mechanism of shunt in atrial septal defect is graphically illustrated in Fig. 1. In the normal subject, the left auricular pressure has been measured and found to be 1 to 5 mm. Hg higher than the right.[5, 6] Consequently in the normal heart the right and left ventricles fill to the same volume (in the presence of the balanced circulation which must exist normally) under different

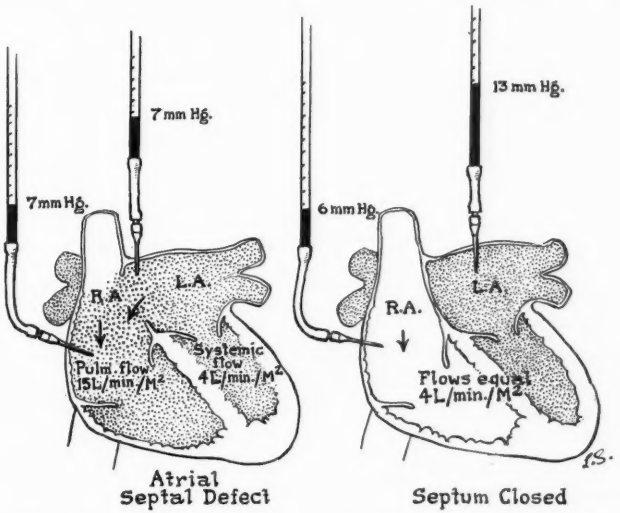

Fig. 1.—Diagram of concept of dynamics of atrial septal defect. With a significant auricular defect, pressures in the two atria are equal; since the right ventricle fills more readily than the left, a shunt through the defect occurs. When the septum is closed the two ventricles have the same output and fill with the same stroke volume under different pressures. Left atrial and ventricular filling pressure may become exceedingly high on closure of the defect.

pressures. In the presence of a large atrial septal defect the pressure in the two auricles is equal and, under such circumstances, the ventricles fill differently with a similar pressure, the right filling more than the left in the uncomplicated case.

This is probably the explanation why pulmonary hypertension is the less frequent accompaniment of atrial septal defect than other communications between the right and left sides of the heart, for as pulmonary resistance increases with associated right ventricular hypertrophy, resistance to filling of the right ventricle increases or the right ventricle fails, and the atrial shunt diminishes. In infants, the thickness of the walls of the two sides of the heart, and hence, probably the resistance to filling, is approximately equal so that in infants the shunt is relatively less than in adults. Only rarely does uncomplicated atrial septal defect cause significant embarrassment to the very young patient.

The observed rise in pressure in the left atrium while pressures in other chambers fell, following closure of atrial septal defect, is further support of this mechanism of the atrial shunt. Of some surgical significance is the fact that left atrial pressure may rise precipitously and strikingly. In 8 of the 21 patients, the mean left atrial pressure rose to 15 mm. Hg or higher. Persistence of this pressure in the left atrium in itself would lead to pulmonary engorgement and edema, and compensation evidently occurs in the postclosure period.

We have been struck by the manner in which intracardiac pressures in patients with an open chest may vary depending upon the condition of the patient's blood loss and replacement. Estimated blood volumes in patients with atrial septal defect have shown an increased volume in the usual instance with a decrease in this volume after closure.[18] Because of this and because of the observed increase in left atrial pressure we have been less vigorous in blood replacement during operation in these than in other patients being treated with cardiovascular disease.

Finally, in contrast to patients with patent ductus arteriosus or ventricular septal defect, the closure of an atrial defect with a large left-to-right shunt may not be entirely innocuous. We have attributed dyspnea (and in one case cardiac asthma) and periods of arrhythmia after repair of atrial defects to left ventricular decompensation, of which we have indication from increased left atrial pressure at operation. Watkins and Gross[19] noted in some patients a transient left ventricular failure which they attributed to a greater ventricular filling pressure after septal repair. The primary defect appears to be in the left ventricle, which in some cases is hypoplastic, and should be treated by restriction of fluid, diuretics, digitalization, and, on some occasions, venesection. Fortunately, in only the occasional patient has this been a significant problem in the postoperative period. Similar studies and conclusions have recently been reported by Pemberton, Kirklin, and Wood.[20]

CONCLUSION

Intracardiac pressures taken during operation for closure of atrial septal defect in 21 patients have been analyzed. In 3 patients with pulmonary hypertension, increased pulmonary resistance and only slight increase in pulmonary blood flow, there was the least change in these pressures. In the remaining cases, the left atrial pressure tended to rise while pressure in other chambers fell following repair of the defect. In 8 of these patients the mean pressure rose to more than 15 mm. Hg. These data support the concept that flow through the defect is due to decreased resistance to filling of the right as compared with the left ventricle.

This elevation of left atrial pressure following repair of the defect seems to be well tolerated by the otherwise normal heart and compensation proceeds rapidly. In some instances subjection of the left ventricle to an unaccustomed high filling pressure may lead to decompensation, especially in the presence of left-sided valvular or myocardial abnormalities.

The surgical significance of these observations would seem to be that such patients should not be overtransfused during operative repair of the defect and

that the occasional patient who shows signs of left ventricular failure postoperatively should be treated with digitalis and measures directed at reducing circulating plasma volume.

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(For Discussion, see page 703)

TRANSPLANTATION OF THE HOMOLOGOUS CANINE HEART

SALEM F. SAYEGH, M.D.* (BY INVITATION) AND OSCAR CREECH, JR., M.D.
NEW ORLEANS, LA.

TRANSPLANTATION of the homologous canine heart is an intriguing laboratory procedure that may find increasing usefulness as an experimental technique. This preparation provides a completely denervated, functioning organ which, because of its accessory role, can be studied without significant effect on the recipient. Besides its value as a physiologic tool, the grafted heart may afford information on the fate of organ transplants and on factors influencing survival. This report concerns the technique of transplantation of fetal and puppy hearts, the mechanism of death of the grafts, and factors which appear to affect survival.

METHODS

Hearts were obtained from newborn pups averaging 800 Gm. in weight and fetuses removed by hysterotomy during the last one or 2 weeks of gestation. Recipients were mongrel dogs averaging 10.4 Kg. in weight. The neck was the site of implantation in all except 3 instances and, in these, the femoral region was utilized. In 2 experiments, the recipient was mother of the donor but in all others the donor and recipient were presumably unrelated.

Following anesthetization with intravenous Nembutal, the external jugular vein and common carotid artery of the recipient were isolated through a longitudinal cervical incision (Fig. 1, *A*). A 3 cm. segment of the sternocephalicus muscle was excised to provide a bed for the graft and to prevent kinking of the vascular pedicle. The technique of implanting the heart into the vascular system of the recipient was essentially that of Mann and associates.[3] The proximal end of the common carotid artery and the distal end of the external jugular vein were ligated. Serrefine clamps were applied and these vessels divided (Fig. 1, *B*). In later experiments with fetal hearts this technique was modified by ligation of the internal carotid artery to reduce blood flow to the graft (see Fig. 3, *B*). When the recipient site was ready, the heart to be transplanted was removed together with the lungs (Fig. 2, A). The pericardium was excised, 5.0 mg. of heparin injected through the superior vena cava, and the venae cavae ligated (Fig. 2, *B*). The lungs were removed after mass ligation of the hilar structures, and aorta and pulmonary artery were isolated and cut to the proper length. The pulmonary artery of the graft was anastomosed to the proximal

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end of the external jugular vein of the recipient with a continuous suture of No. 6-0 silk. Then, the ascending aorta of the graft was anastomosed to the distal end of the common carotid artery of the recipient in a similar fashion (Fig. 3, *A*). Anastomosis of vessels from the fetal hearts was accomplished

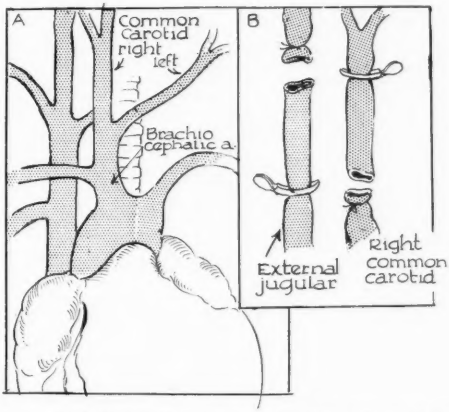


Fig. 1.—Technique of transplantation. The external jugular vein and common carotid artery are isolated (*A*) and prepared for anastomosis to the vessels of the graft (*B*).

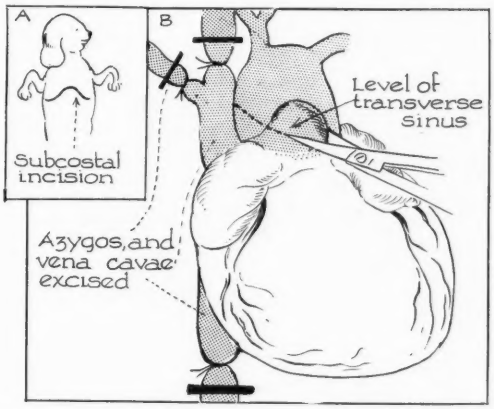


Fig. 2.—Technique of transplantation. With the recipient site prepared, the donor heart is removed through bilateral thoracotomy (*A*). The venae cavae are ligated and aorta and pulmonary artery are divided at level of transverse sinus (*B*).

with No. 7-0 silk. Occluding clamps were then removed and contraction of the transplant began almost immediately. After hemostasis was complete and a sinus rhythm established, the wound was closed with interrupted cotton sutures. In 5 of our experiments the grafted hearts were encased in a semipermeable film at the completion of the anastomoses. Cellophane was used in 3 instances and millipore in 2.

An electrocardiogram was made at completion of the operation and one to four times daily thereafter. Penicillin was administered to the recipients for the first 4 days. When all electrical activity had ceased, as indicated by the electrocardiogram, the graft was removed and fixed in 10 per cent formalin for gross and microscopic examination.

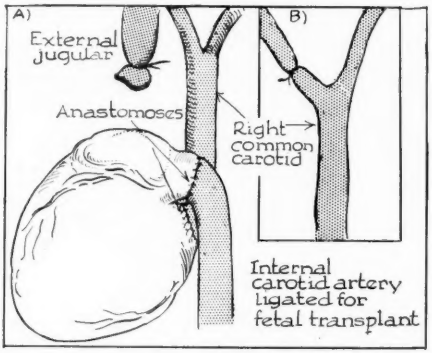


Fig. 3.—Technique of transplantation. The aorta of the graft is anastomosed to the distal end of the common carotid artery, and pulmonary artery to the proximal end of the external jugular vein (*A*). To reduce retrograde blood flow to fetal transplants the internal carotid artery is ligated (*B*).

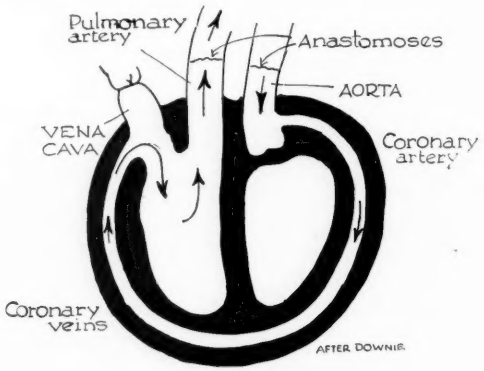


Fig. 4.—Circulation in the graft.

RESULTS

There were 31 experiments in this series. The donors were newborn pups in 21 instances and fetuses in 10.

In the majority of instances, contractions of the hearts ceased within 5 minutes after removal from the donor. The resulting period of standstill during the time required for implantation varied between 15 and 20 minutes. In a few instances, feeble contractions continued while the anastomoses were performed.

The transplants began to contract immediately upon being perfused with arterial blood (Fig. 4). In about 75 per cent of experiments, the initial cardiac

action consisted of ventricular fibrillation which reverted spontaneously to sinus rhythm. With the establishment of a regular rhythm the rate varied between 140 and 200 per minute. This rate persisted until the graft began to fail. In most cases sudden release of the occluding clamp on the carotid artery resulted in distention of the aortic annulus and regurgitation into the excluded left ventricle. This produced extreme distention of the left ventricle and poor function of the heart. For this reason, the carotid artery was opened slowly and the occluding clamp completely removed only when vigorous contractions with a sinus rhythm had been established. When it appeared that retrograde carotid flow was excessive, a ligature was placed about this vessel and tightened sufficiently to reduce the flow.

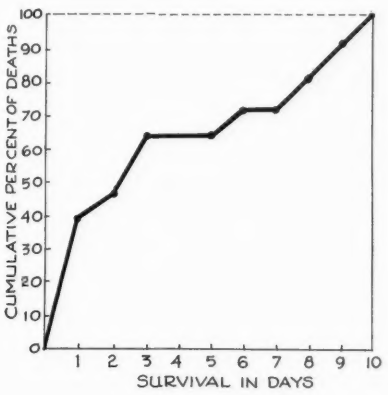


Chart I.

Frequently serum collections had to be evacuated from the neck wounds beginning on the first day after operation and contractility of the transplant improved noticeably after drainage of the wound. In 2 experiments, dehiscence of the wound occurred on the fifth day, the transplants becoming completely exteriorized. In one of these the graft continued to function for 3 days following wound breakdown, whereas in the other, graft failure occurred promptly. One of the recipients died of pneumonia on the first day after operation; the remainder survived the experiments.

In 21 experiments (67 per cent), the transplants failed by the end of the third day following operation (Chart I). In every instance, death of the graft resulted from occlusion of the aorta or pulmonary artery or both, or from distention of the left ventricle by too great a pressure in the carotid artery. That these failures were due to faulty technique is indicated by the fact that 16 (76 per cent) of the 21 early failures occurred in the first 20 experiments. Only fetal or newborn puppy hearts were used for this study and considerable experience and modification of previously described techniques were required for successful transplantation.

In 8 experiments, the heart survived 7 or more days, the longest period of survival being 10 days. Comparison of the survival of fetal and newborn puppy hearts revealed no significant difference. Thus, in 10 fetal transplants the average survival was 73.2 hours, and in 21 puppy transplants 81 hours (Table I).

TABLE I. RESULTS

TYPE DONOR	NUMBER OF EXPERIMENTS	AVERAGE SURVIVAL (HOURS)
Fetus	10	73.2 (12-204)
Puppy	21	81.0 (12-240)

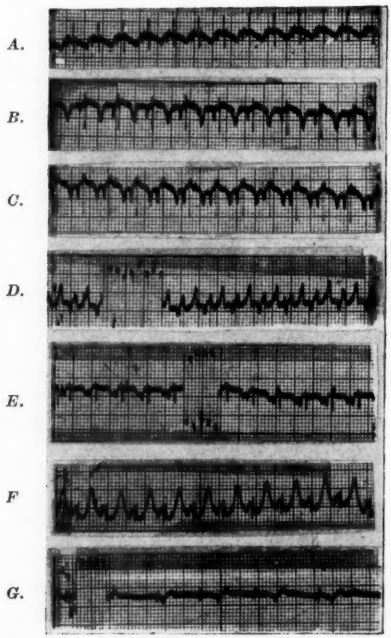


Fig. 5.—Electrocardiographic pattern observed in "ischemic failure" of the transplant. The tracings were made immediately (*A*), 24 hours (*B*), 32 hours (*C*), 48 hours (*D*), 56 hours (*E*), 61 hours (*F*), and 72 hours (*G*) after operation.

Of the 2 grafts encased in millipore, one functioned only 12 hours when death of the recipient occurred, and the other survived 60 hours. However, this material deteriorated so rapidly that it could not have influenced survival of the transplant. On the other hand, 3 grafts wrapped in Cellophane lived 10, 8, and 9 days, respectively.

The groin proved to be unsuitable as an implantation site owing to the lack of a suitable bed for the graft and the propensity of this region for infection.

Among the 8 grafts surviving 7 or more days, there were 2 from fetal donors weighing 250 Gm. each, 3 each from pups weighing 700, 800, and 900

Gm., respectively. None of the transplants from donors weighing less than 250 Gm. or more than 900 Gm. lived more than 3 days.

Serial electrocardiograms revealed three patterns of death. The first was observed primarily in grafts dying within the first 3 days and has been designated "ischemic failure." The electrocardiograms obtained in Experiment 12 demonstrate this pattern (Fig. 5). Thus, depression of the S-T segment was evident immediately after completion of operation (Fig. 5, *A*). On the day following operation, there was elevation of the S-T segment, a varying P-Q interval, an inverted T wave, a wide Q wave, and low voltage (Fig. 5, *B*). This suggests

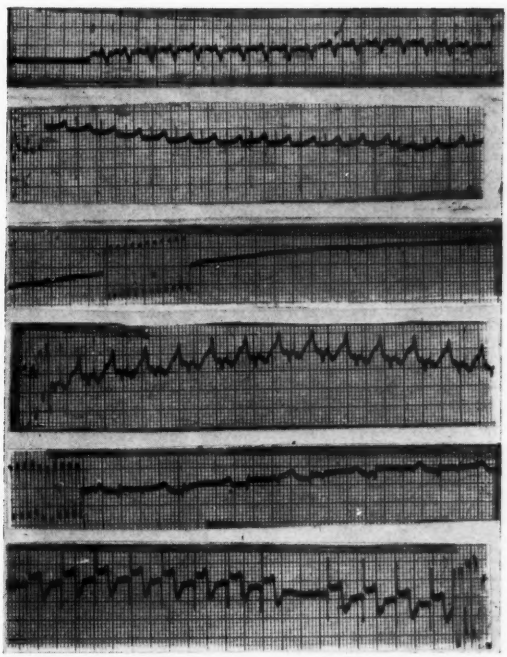


Fig. 6.—Electrocardiographic pattern observed in "mechanismal failure" of the transplant. The tracings were taken 4 hours (*A*), 35 hours (*B*), 48 hours (*C*), 146 hours (*D*), 171 hours (*E*), and 215 hours (*F*) after operation.

acute ischemia and complete heart block with an idioventricular rhythm. On the following day, there was ventricular rhythm indicating further ischemic damage to the transplant (Fig. 5, *F*). Death occurred shortly after the last electrocardiogram was made (Fig. 5, *G*).

The second type of electrocardiographic pattern observed suggested "mechanismal failure." The tracings obtained in Experiment 15 are examples of this type (Fig. 6). Comparison of the pattern immediately after transplantation with the preoperative electrocardiogram reveals that the P waves, QRS complex and T wave were in the opposite direction from those obtained prior to operation. This was probably due to the position of the heart in the recipient.

Thus, these electrocardiograms may be interpreted as mirror images of themselves (Fig. 6, *A*). There was depression of the S-T segment immediately after operation suggesting myocardial injury. On the second postoperative day there was an R_1 wave and a diphasic T wave suggesting right ventricular strain (Fig. 6, *B*). On the sixth postoperative day, an elevated S-T segment suggested myocardial injury (Fig. 6, *D*), and on the eighth day the electrocardiogram revealed a wide T wave, A-V block, and low voltage (Fig. 6, *E*). This was followed by the development of idioventricular rhythm and death (Fig. 6, *F*).

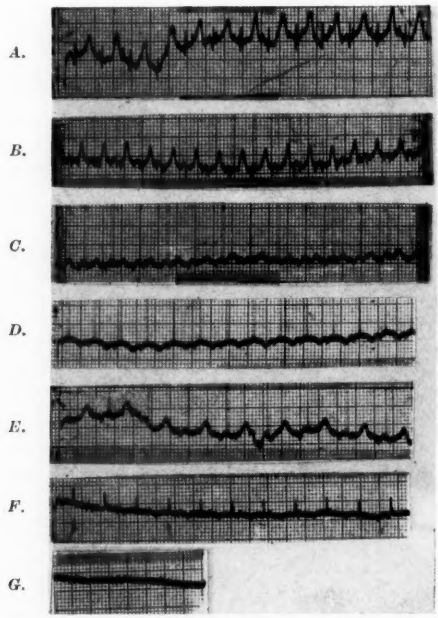
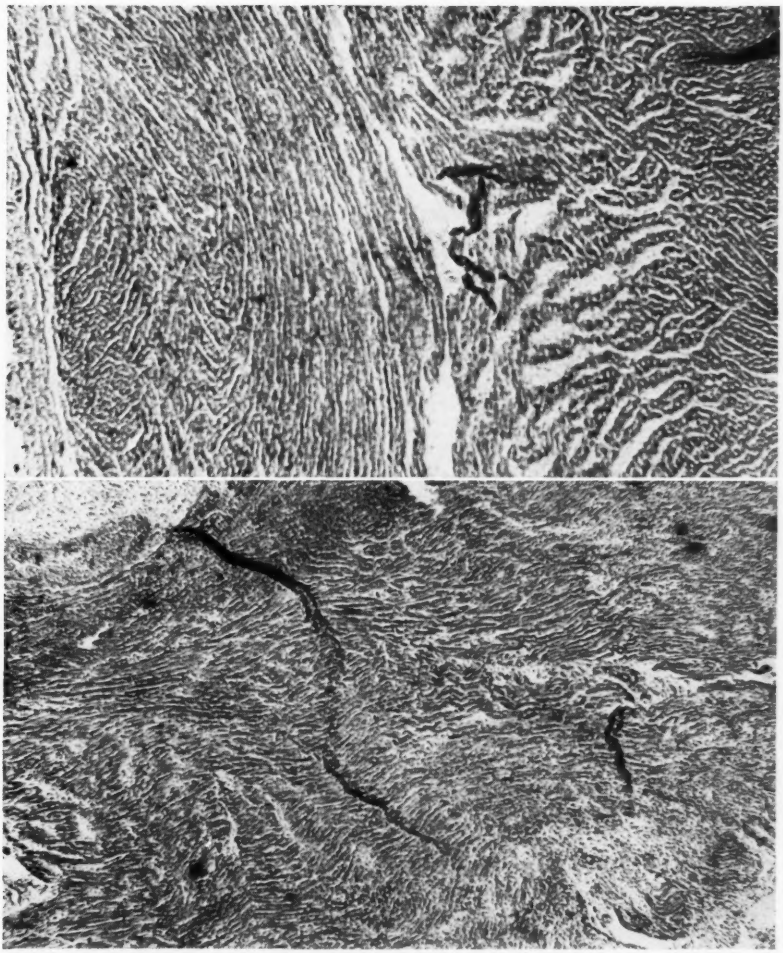


Fig. 7.—Electrocardiographic pattern observed in "reactive failure" of the transplant. The tracings were taken immediately after operation (*A*), 48 hours (*B*), 96 hours (*C*), 144 hours (*D*), 168 hours (*E*), and 192 hours (*F*) after operation. *G* represents the recipient heart tracings recorded at the site of transplant.

The third type of failure has been designated "reactive failure" on the basis of the electrocardiograms. Experiment Number 27R is an example of this type (Fig. 7). Immediately after operation there was good amplitude, evidence of a supraventricular pacemaker, and a rate of 200 per minute (Fig. 7, *A*). On the second day after operation the amplitude somewhat decreased and the rate was now 240 per minute (Fig. 7, *B*). On the seventh day the rate had decreased to 140 per minute and the T wave was again upright (Fig. 7, *E*). An electrocardiogram on the sixth day revealed a very wide T wave and loss of amplitude of the QRS complex (Fig. 7, *D*). On the day of death of the transplant (eighth day), the amplitude of the QRS complex was quite low and the rate 170 per minute (Fig. 7, *F*).

Gross examination of the transplants after death revealed changes which varied with the period of survival and the cause of death. Thus, the grafts examined within 3 days after implantation were covered with a thin layer of fibrin. In the absence of thrombosis of the pulmonary artery the myocardium appeared pink and relatively normal. With thrombosis of the vascular pedicle, the myocardium was dark red and congested. When carotid artery pressure was great enough to dilate the aortic annulus, the left atrium and ventricle were

A.



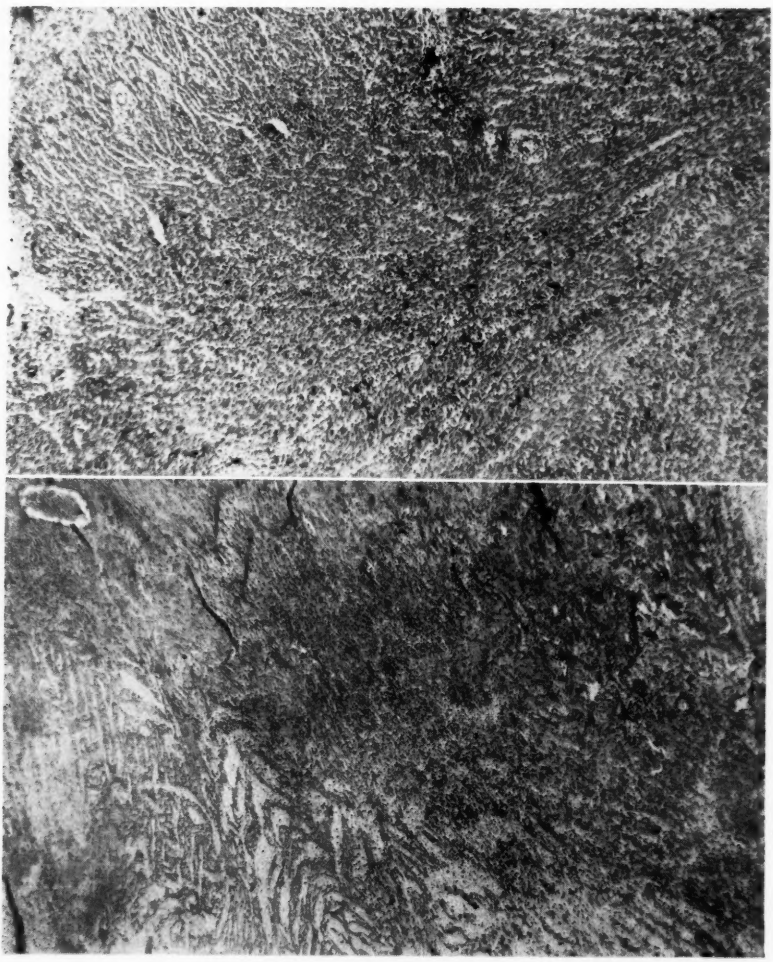
B.

Fig. 8.—Microscopic examination of the transplanted canine heart: *A*, At 30 hours after operation, edema and round-cell infiltration of the myocardium are revealed. *B*, 72 hours after operation there is focal necrosis of the myocardium and hemorrhage between the muscle fibers.

distended with thrombi and the myocardium was congested. Grafts surviving 5 or more days were covered with a thick layer of fibrin and the myocardium was swollen and soft. In some instances the entire graft was necrotic.

Microscopic examination of the transplants removed one to 10 days after operation revealed rather characteristic changes depending upon the length of survival. Thus, in grafts surviving 30 hours or less there were areas of acute infarction in the myocardium with extensive infiltration of polymorphonuclear

C.



D.

Fig. 8.—Cont'd. Microscopic examination of the transplanted canine heart: *C*, Further deterioration of the myocardium is observed at 144 hours after operation. *D*, After 240 hours there is almost complete necrosis of the transplant.

leukocytes (Fig. 8, *A*). Subepicardial hemorrhage was evident in places and the muscle fibers were spread apart by edema fluid and polymorphonuclear leukocytes. On the third day, there was extensive fibrinous deposits covering the entire epicardial surface, with early connective tissue invasion in places (Fig. 8, *B*). The myocardium was extensively infiltrated with inflammatory cells and early degeneration of muscle fibers in the mid-zone areas was noted. Muscle fibers were spread apart by edema fluid and collections of erythrocytes. On the sixth day, round-cell infiltration of the myocardium was more extensive (Fig. 8, *C*). The fibrinous layer on the epicardium was thicker and showed evidence of early organization. There was moderate degeneration of muscle fibers. These changes rapidly progressed and by the eighth day there were generalized degenerative changes in the entire graft (Fig. 8, *D*). In almost every instance there was a thrombus in the excluded left ventricle. In the graft which functioned for 10 days, a thick fibrin layer covering the surface of the heart was extensively infiltrated with fibroblasts. There were many areas of acute infarction with various stages of degeneration in the muscle fibers. A small mural thrombus was noted inside the left ventricle. In some areas in which muscle degeneration was most marked there was fatty infiltration.

Almost invariably the septal tissue was noted to be less involved by the changes described above than other portions of the myocardium, and the conductive tissue appeared to be least affected of all.

DISCUSSION

Among studies of organ transplantation, the heart has received relatively little attention. The experiments of Alexis Carrel[1] in 1907 were the earliest recorded. The details of the technique are lacking; however, it appears that the heart was transplanted to the neck, anastomoses being made between the jugular vein and the carotid artery of the recipient and the aorta, pulmonary artery, pulmonary veins, or one of the venae cavae of the donor.

In 1933, Mann and associates[3] described a technique for cervical transplantation of the homologous canine heart which has been employed in most of the experiments since that time. The longest survival reported by Mann was 8 days with an average survival of 4 days.

A new technique of transplanting the canine heart was reported by Sinitsyn[7] in 1948. This method consisted of anastomosis of the left auricular appendage of the graft to the proximal end of the divided carotid artery of the recipient, the aorta or brachiocephalic artery of the graft to the distal end of the common carotid of the recipient, and the pulmonary artery of the graft to the proximal end of the external jugular vein of the recipient. Thus, the coronary circulation of the transplant is provided by the action of its own left ventricle.

Utilizing the method of Mann and associates, Downie[2] performed 30 canine heart transplantation experiments, 23 of which were successful. The average weight of the donors was 2.7 Kg. The longest survival was 250 hours with an

average of 129 hours. In 5 experiments, Downie transfused the recipient with blood from the donor prior to operation and these transplants survived somewhat longer than the rest.

The electrocardiographic and morphologic changes occurring in the transplanted hearts of dogs have been described by Wesolowski and Fennessey.[8] They observed that the amplitude of the QRS complex progressively diminished with the survival of the graft and attributed this to edema and fibrin deposited about the graft. The microscopic appearance of 7- to 10-day-old transplants was characterized by complete degeneration, necrosis, and liquefaction. Somewhat similar studies by Marcus, Luisada, and Wong[4, 5] suggest that the morphologic changes are the result of tissue incompatibility which was unaffected by altering the technique of transplantation or by interim parabiotic perfusion.

The experiments reported here are the first in which newborn pups and fetuses have been used as donors. It was hoped that fetal hearts would be less antigenic than hearts of older animals and that the survival time of the transplant would be longer. This did not prove to be the case, however. In fact, hearts from newborn pups weighing 700 to 900 Gm. functioned best. It should be pointed out that these experiments do not serve to evaluate the antigenicity of homologous fetal myocardium since most of the failures in this group were technical in nature or resulted from overloading a fragile and immature organ. Improved methods for transplanting the fetal heart have been developed and should make possible a more critical evaluation of survival.

The relatively long survival time of 3 transplants wrapped in Cellophane suggests that the local tissue reaction resulting in deposition of fibrin on the epicardial surface may be an important factor in the death of the graft. The improvement observed frequently in electrocardiographic patterns following evacuation of collections of serum from the wound is an additional factor in support of this concept. Ideally, the transplanted heart should be excluded completely from surrounding tissues since it is not dependent on them for its blood supply. In this way, contractions of the heart muscle continue until some intrinsic interference occurs.

In many respects, the homologous heart graft is a more satisfactory preparation for the study of factors influencing homograft survival than is the kidney. The function of the transplant can be readily detected and morphologic changes occurring in the graft are reflected in the electrocardiogram.

SUMMARY

Thirty-one homologous transplantations of the canine heart were performed. The donors were fetuses obtained by hysterotomy in 10, while the remainder were newborn pups.

The ascending aorta and the pulmonary artery of the graft were anastomsed to the distal common carotid artery and proximal jugular vein of the recipient, respectively.

In 8 experiments, the heart survived 7 or more days. The average survival for fetal transplants was 73.2 hours, and 81 hours for puppy hearts. Maximum

survival was 10 days. Collections of serum, excessive blood flow to the graft, and infection reduced the survival time.

Protection of the graft from local tissue reaction appeared to prolong survival.

Three distinct electrocardiographic patterns were observed in the transplants and were correlated with morphologic changes.

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Discussion

(Papers by Shumway [page 643], Julian [page 654], Glover [page 661], Benjamin [page 679], Williams [page 685], Sayegh [page 692] and Their Associates)

DR. ARTHUR M. VINEBERG, Montreal, Quebec.—(This discussion was not returned. —Editor.)

DR. SAMUEL A. THOMPSON, New York, N. Y.—The proof of the pudding is in the eating. Our clinical experience with this procedure is limited to 19 cases. In 8 cases it was used as a single procedure and in 11 cases it was combined with cardiopexy. The immediate postoperative reaction is very satisfactory so far as relief of pain is concerned, but we have no long-term follow-up. We believe that there is an additional shunt of blood with increased vascularity to the pericardium following ligation of the internal mammary artery. We believe, however, that the full value of this increased vascularity cannot be realized unless there is some connection, such as intimate contact of the pericardium to the myocardium beyond the point of coronary obstruction. In the light of our very limited experience, we believe that mammary ligation may be useful in the very early cases of coronary disease, or in the very late cases with severe complications where major surgery cannot be tolerated. In the moderately advanced coronary cases, as well as those of myocardial ischemia, we believe the best results will be obtained when mammary ligation is used in combination with some other procedure such as cardiopexy. Cardiopexy furnishes the necessary vascular bridge between the myocardium and the pericardium. Our present experience leads us to believe that the procedure of internal mammary artery ligation does have value, and we plan to continue its use unless later experience gives some contrary indication.

DR. WILLIAM H. MULLER, JR., Charlottesville, Va.—I should like to discuss the very nice work presented by Drs. Williams and Bahnson. We have carried out similar determinations on some 17 patients undergoing closure of atrial septal defects, except that we have not correlated these determinations with the degree of shunt flow.

(slide) This slide shows the determinations which we obtained in our cases. In most instances, the right auricular pressure diminishes after the shunt has been obliterated and this

pressure likewise diminishes in the right ventricle. We found a significant increase in left auricular pressure in some instances after obliterating the shunt, but we have not attached the same significance to this finding as have Drs. Williams and Bahnson.

(slide) This slide shows that there is usually a significant decrease in right auricular and right ventricular oxygen saturation after the defect is closed. There is no significant change in the left auricular oxygen saturation.

(slide) This slide demonstrates that the blood volume usually diminishes by about 20 per cent after the defect is closed. These measurements were obtained one day before and 2 weeks after the defect was closed, utilizing the T-1824 Evans blue dye method. For this reason we have been somewhat reluctant to transfuse these patients up to their preoperative circulating blood volume after the defect is closed.

DR. MOORE.—(This discussion was not returned.—EDITOR.)

DR. ADRIAN KANTROWITZ, Brooklyn, N. Y.—I rise to discuss Dr. Glover's paper. Since this procedure was suggested, we have been interested in studying some of the possible mechanisms for increased coronary blood flow by ligation of the internal mammary artery.

(slide) As Dr. Glover has pointed out, presumably the pathway for improved flow of blood to the myocardium would be by way of the pericardiophrenic arteries which arise from the internal mammary arteries and thence by anastomoses to the coronary arteries. This is essentially a Y arrangement and if you would ligate the internal mammary artery at this point this would presumably improve the blood flow to the pericardium and collaterals.

The flowmeter we have available to us in the laboratory was not small enough to insert into either the internal mammary artery or the pericardiophrenic artery; so we chose an anatomic situation which was approximately the same. That is, the bifurcation of the aorta, which again is a Y arrangement. According to the thinking presented by the speaker, clamping one iliac artery should shunt more blood to the other iliac artery. We inserted our instruments to measure blood pressure and flow to the left iliac artery, and recorded these variables while we clamped and unclamped the right iliac artery. It should be remembered that there is a rich anastomoses between these two vessels, below the point of clamping through the hypogastric arteries.

(slide) The upper tracing is the recording of left iliac blood pressures, the lower tracing is the recording of blood flow through this vessel. At this point the contralateral iliac artery is clamped. There is a momentary rise in blood pressure for one or two heartbeats and an associated momentary increase in blood flow. Then there is a slight drop in blood pressure for perhaps 15 or 20 seconds, again associated with a small decrease in blood flow.

As you see, however, both tracings very quickly stabilize at approximately the preclamping control levels.

When the contralateral artery is unclamped there does not seem to be any appreciable change, in pressure or flow.

We have concluded from this experiment, then, that for this situation we have no evidence that would indicate that occluding one artery would significantly alter pressure or blood flow in the other.

DR. ROBERT KLOPSTOCK, Brooklyn, N. Y.—(This discussion was not returned.—EDITOR.)

DR. ANDREW G. MORROW, Bethesda, Md.—We have also been interested in the changes in left and right heart pressure following septal defect closure as described by Dr. Williams and Dr. Bahnson. However, we have collected our data in a somewhat different fashion.

In patients being operated upon with hypothermia or extracorporeal circulation, a catheter is passed into the right ventricle before operation. As soon as the chest is opened another catheter is passed via a segmental pulmonary vein into the left atrium. Thus, the arterial pressure, right ventricular and left atrial pressures can be recorded for 24 hours.

Here are such measurements in a patient with an atrial septal defect operated on with hypothermia. You will see that as the patient cools there is a fall in ventricular filling pressure. With manipulation of the heart and passing the caval ligatures the pressures rose strikingly. In the immediate postocclusion period there are striking elevations in the left atrial pressure, but in the course of 6 or 8 hours it gradually returns to normal, confirming what Dr. Williams suggested.

I would be particularly interested to know if data concerning digitalis are available, and if their patients who showed these elevations were digitalized.

DR. B. L. BROFMAN, Cleveland, Ohio.—As a so-called cardiologist, I rise primarily to applaud the intensification and expansion of the surgical onslaught against coronary heart disease, with particular reference to the resourcefulness and ingenuity of Dr. Julian's group and others. The catastrophic consequences of this relentless occlusive process in the coronary arteries, as manifested by increasing invalidism and exorbitant mortality, have attained such proportions that relative medical complacency should be replaced by generalized alarm to stimulate far greater efforts as warranted by the extent of the devastation associated with this disease. By its very nature, coronary heart disease defies "objective" evaluation, and hence the validity of any medical or surgical treatment is necessarily difficult to establish, keeping in mind that controversy has continued to rage for years over many fundamental concepts in coronary disease.

In our desire to achieve the "direct" surgical approach to this disease, we must not disregard certain fundamental (but neglected) considerations with regard to the pathophysiology of coronary heart disease. Unfortunately, the remarkable technical accomplishment of coronary arterial anastomosis and of coronary endarterectomy is of relatively little significance as compared to the more formidable problems inherent in the "direct" approach. Presumably, contrast visualization of the coronary arteries in man will eventually be feasible (if somewhat dangerous); thus, in a patient with clinical symptoms of coronary heart disease, "localization" of obstructions in the coronary circulation will allow the surgeon to select at least the most "significant" diseased segment for the "direct" approach. (I do not believe we can anticipate the application of this procedure to more than one or perhaps two separate obstructions in a given patient.) Unfortunately, it is axiomatic that *there is no obligate relationship between the extent and location of the occlusive process in the coronary arteries and the clinical consequences thereof.* Only "moderate" stenosis of one artery may result in death; on the other hand, chronic multiple complete occlusions of two or more arteries may produce no symptoms and no myocardial damage. In a fundamental sense, the patient's symptoms are *not* due to the actual occlusive process in the coronary arteries, but to the response of the myocardium.

In a patient with coronary heart disease, the unwarranted assumption that the functional disturbance is due to a given obstruction of a coronary artery is most ill-advised, and may have disastrous consequences. Restoration of flow into a given area of myocardium may not only have no beneficial effect, but, if flow is restored to a scar in a previously infarcted region, preferential perfusion of a low-resistance area may deprive viable myocardium of critically needed blood, so that a deleterious effect is produced.

The patient with coronary heart disease has a precariously balanced circulation; adequate intercoronary collaterals may maintain the dynamic integrity of the heart almost indefinitely. Any procedure which enhances the production of collaterals *in advance* of the occlusive process will be remarkably effective. On the other hand, a "direct" approach, which may actually disrupt this balance, may have catastrophic consequences.

DR. FRANK GERBODE, San Francisco, Calif.—I want to discuss Dr. Bahnson's paper. We have not routinely measured intra-atrial pressures during operation for the closure of atrial septal defects, but I believe this may be quite important in some cases. We have had at least three instances of left ventricular failure in our atrial closures. Two patients developed failure after closure of rather large septal defects with low pulmonary vascular resistance. Both required hospitalization for some weeks after closure of the intra-atrial septal

defect, but fully recovered. This means, therefore, that one must be on the lookout for this later, after the immediate postoperative course. We have been very careful about transfusing patients during and immediately following operation for those reasons. The one death in our last 35 atrial closures was in a poorly developed child who had an atrophic left ventricle and a considerably smaller mitral than tricuspid valve.

DR. ORMAND C. JULIAN, Chicago, Ill.—I should like to make two comments, one on Dr. Moore's mention of thrombosis. One of the results of our work seems to indicate that, if the long mammary artery was used, thrombosis is a complication, whereas if the small homogeneous graft, larger in diameter, is used, thrombosis did not occur. Dr. Brofman has raised the problem of possible clinical use of this technique if we could once get it to work in 100 per cent experiments. Where would the end of the graft be implanted? There would be two possibilities, one being that one should implant the graft distal to the obstructed area, just as we do in the case of lower extremity arteriosclerosis; the other might be that one should use the graft to increase the pressure proximal to the obstruction wherever it may be, perhaps even the left coronary artery in toto being the recipient of this grafted blood supply.

DR. ROBERT P. GLOVER, Philadelphia, Pa.—I should like to thank the several discussants. It must be obvious that in the early stages of this program of internal mammary artery ligation for increasing myocardial blood flow, neither authors nor discussants have much experience to fall back upon. The paper was given not only to present our initial attempts to corroborate the findings of the Italian workers but also to stimulate interest and thinking in the complex field of coronary arterial disease. It is quite understandable that Dr. Vineberg might find this procedure objectionable for on the surface it seems to be diametrically opposed to his procedure of implantation of the very same artery into the myocardium. I must emphasize the fact that I am not promoting this procedure, as he has implantation of the mammary artery, but merely trying to find out whether it has value. Undoubtedly in a condition so insidious and variable as coronary artery disease evaluation will take years.

Dr. Thompson is to be particularly commended for his attitude and well-spoken comments. His procedure of pericardial poudrage has been used by him and others for years. Undoubtedly it has merit yet he has taken the trouble to try this newer and even more innocuous method. I agree with his observation that, ultimately, mammary artery ligation as presented may find its proper place as an adjunct to other procedures. In the meantime, however, it is essential to evaluate it extensively, both experimentally and clinically, on its own merits as a single operative procedure.

DR. G. RAINEY WILLIAMS, Baltimore, Md.—In answer to Dr. Morrow's question with regard to digitalization of patients with elevated left atrial pressures at the time of operation, we have not digitalized such patients unless further clinical evidence of failure was present. Patients with atrial septal defects, without failure, have not been digitalized preoperatively as digitalis is said to increase the left-to-right shunt.

We should like to thank the other discussants for their comments.

Announcements

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Thirty-eighth Annual Meeting of the American Association for Thoracic Surgery will be held May 16, 17, and 18, 1958, in Boston, Massachusetts. Headquarters will be at the Hotel Statler.

Requests for Hotel Reservations

These should be mailed directly to Mr. F. Whitehouse, Front Office Manager, Hotel Statler, Park Square, Boston, Massachusetts. Please mention this Association, the type of accommodation desired, the date, and approximate hour of arrival and departure. If accommodations are desired elsewhere in Boston, please communicate directly with the hotel of your choice.

Thoracic Surgery Forum

The Thoracic Surgery Forum will be continued as a special session at the 1958 meeting. The Forum is primarily for the presentation of short papers on current thoracic research, experimental problems, anatomical studies, and modified or new surgical techniques. The inclusion of any considerable amount of clinical material in these reports makes them unsuited for this session.

Papers at this session will be limited to ten minutes, including the showing of lantern slides or other illustrative material. At the discretion of the President, three minutes may be allowed as the maximum discussion for each paper.

All Thoracic Surgery Forum papers will be published together in one issue of the JOURNAL. Maximum length: 3,000 words without illustrations. If illustrated, an appropriate number of words must be subtracted for each cut used.

Abstracts of Papers

Abstracts of all papers for presentation at the 1958 meeting must be received on or before Dec. 15, 1957, otherwise they will not be considered by the Program Committee.

Abstracts should be labeled "For Thoracic Surgery Forum," or "For Regular Program." They should contain from 200 to 250 words and accurately reflect the content of the completed paper.

Six, repeat, six clearly legible copies of *each* abstract must be sent to Miss Ada Hanvey, Administrative Assistant, The American Association for Thoracic Surgery, 600 South Kingshighway, St. Louis 10, Missouri.

Essayists selected for the program are reminded that papers presented at the meeting *must* be handed to the secretary immediately after their presentation. If they are not ready at that time there is a chance that they will not be published in THE JOURNAL OF THORACIC SURGERY.

Motion Picture Session

Provisions have been made to show a limited number of motion pictures to be selected on a competitive basis. *The films themselves,* together with descriptive material concerning length of presentation, etc., must be received by Dr. Karl P. Klassen, The Ohio State University, Columbus 10, Ohio, before Dec. 15, 1957.

It is planned to run the motion pictures in a smaller room at the same time as the scientific sessions. If the films are well labeled, it will not be necessary for the author to be present for comment.

Applications for Membership

Applications for Associate Membership in the Association must be received by the Membership Committee not later than Dec. 15, 1957, otherwise the application will be deferred for consideration until the 1959 meeting.

Applicants must be sponsored by three Active or Senior Members of the Association. In addition to the signatures on the application form, the sponsors will forward a *separate* letter concerning the applicant directly to:

Dr. Duane Carr
Chairman of the Membership Committee
899 Madison Avenue
Memphis, Tennessee

Sponsors are reminded that *new* letters of recommendation must be forwarded to the Membership Committee should their applicants be held over for reconsideration a *second year.* The new letters of recommendation should also be sent to Dr. Carr, the Chairman of the Membership Committee.